UNIVERSITY OF UTAH
COLLEGE OF PHARMACY
L. S. SKAGGS PHARMACY INSTITUTE

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ABUSE AND MISUSE OF GABAPENTIN

Drug Regimen Review Center

Joanita Lake B.Pharm, MSc EBHC (Oxon), Research Assistant Professor
Lauren Heath, Pharm.D., MS, BCACP, Assistant Professor (Clinical)
Valerie Gonzales, Pharm.D., Clinical Pharmacist
Vicki Frydrych, B.Pharm., Pharm.D., Clinical Pharmacist
Elena Martinez Alonso, B.Pharm., MSc MTSI, Medical Writer
Stephen Kim, Pharm.D. student
Angela Clayton, Pharm.D. student
Joanne LaFleur, Pharm.D., MSPH, Associate Professor

Data support
Jacob Crook, MStat

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Contents

Introduction

Drug overdose is the leading cause of accidental death in the US (70,237 drug overdose deaths occurred in the United States in 2017) and of these 67.8% of deaths are related to opioids.[1,2] The most recent emergency department data from the fourth quarter of 2017 to the fourth quarter of 2018 show Utah is one of five states with significant increases in all suspected drug overdoses.[3] Drugs other than opioids contribute to the alarming number of overdoses.[3] Frequently, several drugs are involved in overdose cases and the contribution of each drug to the person's death cannot be determined from the literal text analysis of death certificates.[4,5] The role of gabapentin in the drug overdose epidemic is unclear.

In an effort to curb opioid use, the Centers for Disease Control and Prevention (CDC) *Guideline for Prescribing Opioids for Chronic Pain* recommends nonpharmacologic therapy and nonopioid pharmacologic therapy as preferred for the treatment of chronic pain and that opioid use is considered only if "expected benefits for both pain and function are anticipated to outweigh risks to the patient."[6] They also recommend combining opioids (if used) with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate (recommendation category: A, evidence type: 3).[6] Chronic pain refers to pain lasting more than 3 months or past the time of normal tissue healing.[6] Also, these recommendations are not intended for pain during active cancer treatment, palliative care, or end-of-life care.[6] The CDC states that "[c]ontinued efforts to ensure safe prescribing practices by following the CDC Guideline for Prescribing Opioids for Chronic Pain are enhanced by access to nonopioid and nonpharmacologic treatments for pain."[2] However, the CDC cautions against aggressive implementation of the guideline (e.g., immediate and aggressive opioid tapering) due to the potential for patient harm.[7]

Gabapentin was previously thought to not have abuse potential, but evidence to the contrary is emerging. Restricting opioid prescribing, and encouraging nonopioid treatments for pain, may be facilitating increases in gabapentin prescriptions and abuse. The Drug Enforcement Administration (DEA) reported an increase in problematic gabapentin use in recent years.[8] It has been "…increasingly encountered by law enforcement, documented in national crime lab reports, reported to poison control centers, and diverted for illicit use."[8] Gabapentin may be misused for recreational use (to get "high" or increase a "high" when taken with opioids or other medications), self-medication (for pain or withdrawal symptoms), or self-harm (suicide).[9] In 2017, there were 6,722,145 prescriptions (IMS Health™) dispensed for gabapentin in the US which has doubled since 2011.[8] More patients are being exposed to gabapentin, frequently for off-label use, increasing the risk of gabapentin abuse. Possible reasons for the increasing use and abuse include the ease of obtaining prescriptions for large quantities and low cost (it has been referred to as a 'cheap man's high'[9]).[10] Several other factors also increase this risk of abuse such as misunderstandings of abuse potential amongst prescribers.[10]

The main focus of this review is the safety and appropriate use of gabapentin. We aim to:

(A) Review evidence of gabapentin misuse and abuse worldwide, and in Utah specifically, to determine the extent of the problem including the following:

a) Prevalence
b) Populations at increased risk for abuse/misuse
c) Sources of abused or misused gabapentin, and street market
d) Doses needed for effects sought by abusers or misusers
e) Toxic effects, drug overdoses, and management of intoxication
f) Factors increasing the abuse effect/risk of overdose

(B) Review product information, tertiary data sources (electronic databases e.g., Micromedex, Lexicomp), and other sources of expert information for information regarding FDA-labeled indications and select drug-drug interactions, including both pharmacokinetic and pharmacodynamic issues.

We will not be reviewing the appropriateness of off-label uses including use in the treatment of substance use disorder, but information will be included to explain its place in therapy.

(C) Review national and local (Utah) data and statistics (e.g., CDC and Poison Control exposure data) to provide further insight into gabapentin use in Utah.

(D) Review gabapentin utilization in the Utah Medicaid population to determine whether potentially inappropriate use is a problem

Ultimately, the purpose of this review is to help reduce inappropriate use and prescribing (if it is a problem).

Background

Gabapentin is FDA-approved as adjunctive therapy in the treatment of epilepsy (partial onset seizures, with and without secondary generalization) in patients >3 years old, and for the treatment of post-herpetic neuralgia in adults.[11] Gabapentin enacarbil extended release tablets (Horizant) is indicated for treatment of moderate-to-severe restless leg syndrome (RLS) and postherpetic neuralgia (PHN) in adults.[12] Other uses of gabapentin are off-label. Some off-label indications are with supportive evidence and clinical guidelines recommending their use (neuropathic pain, post-operative pain, alcohol use disorder, chronic refractory cough, and migraines, to name a few).[12,13] Gabapentin is structurally related to pregabalin (a schedule V drug) in that they both contain GABA, but gabapentin has a lipophilic cyclohexyl group attached to GABA.[8] Gabapentin has analgesic and antiepileptic actions, but its exact mechanism of action is unknown.[8]

Gabapentin does not bind to $GABA_A$, $GABA_B$, opioid, benzodiazepine or cannabinoid receptors (at clinically therapeutic doses of 900-3600 mg/day) although it can increase GABA levels (dose-dependently with a modest increase of extracellular GABA in brain[14]) and decrease glutamate concentrations.[15,8,16,17] Because of this, the gabapentin drug approval process did not require abuse-potential assessment and it is not currently controlled under the Federal Controlled Substances Act of 1970. Gabapentin is not a controlled substance in most states. The exact mechanism of gabapentinoid abuse is not fully understood,[10] but it is thought to be related to the weak GABAmimetic activity which may cause relaxation and euphoria, especially at the beginning of therapy and during an overdose.[14] Usually increases in dopamine plays a role in the addictive power of drugs, and according to authors of a recently published systematic review, there is currently no evidence indicating gabapentinoids may cause this action in the mesolimbic reward system.[14] However, they state that neuroimaging studies to evaluate this are warranted.[14] Nonetheless, due to increases in prescribing and abuse, it has been classified as a Schedule V controlled substance at a state level (not federal level) in Kentucky (July 2017), Tennessee (July 2018), Michigan (January 2019), and Alabama (November 2019), with more states considering this change.[18-22] In Utah, the Board of Pharmacy requested the Controlled Substances Advisory Committee (CSAC) to consider a recommendation to schedule gabapentin in the Utah Controlled Substances Act as a Schedule V controlled drug based on national trends in the misuse and abuse of gabapentin.[23] Because it is unclear if gabapentin is being abused in Utah, but possible, the CSAC

2019 Legislative Recommendations to the Members of the Health and Human Services (HHS) Interim Committee was that gabapentin dispensing data be required for the controlled substances database, and evaluated to determine if it should be scheduled as a controlled substance next year (2020 legislative session).[23] Since December 2016, Ohio required gabapentin data be entered into their Ohio Automated Rx Reporting System (OARRS).[24] In December 2017, Ohio implemented a rule that requires prescribers to include the days' supply (ie, minimum number of days) that the prescription for a controlled substance (CS) or gabapentin should last the patient.[25] It appears that there is a rule allowing processing of a prescription without this information, but the pharmacy has to follow requirements for reporting days' supply.[25]

This is not the first drug that was thought to have no abuse potential until much later after approval.[10] The abuse potential of benzodiazepines and Z-hypnotics also took several years to be fully appreciated.[10,26] This may have resulted from trials excluding patients with substance use disorders that could have signaled this risk.[10,27,28] Some experts suggest that perhaps abuse liability-focused premarketing studies should consider interaction with alcohol and other drugs as well as routine postmarketing surveillance to assess abuse potential of all new drugs with central nervous system (CNS) activity.[26,29-31]

Methodology

A literature search was developed to identify all systematic reviews and meta-analyses worldwide that reported gabapentin misuse and/or abuse in any population. We also searched for Drug Enforcement Administration (DEA) Drug and Chemical evaluations, and any publication types providing information specific to Utah. We searched Pubmed, Epistemonikos, the DEA website, and the CDC website in November 2019. The Pubmed Medline and Epistemonikos search strategies are included in the supplementary appendix. Search strategies consisted of controlled vocabulary, such as medical subject headings (i.e., MeSH and EMTREE terms), in combination with text words. Search terms were gabapentin AND (abuse OR misuse OR non-medical or nonmedical OR illicit OR addict OR addiction OR diversion OR dependence OR drug-seeker OR drug-seeking OR trafficking OR inappropriate OR overprescribing OR overprescriber or overprescribers OR overtreating OR overdiagnosis OR high). Systematic reviews search filters from Pubmed[32] and adapted by Dalhousie university libraries[33] from SIGN[34] were used. We searched the FDA website, the Substance Abuse and Mental Health Services Administration (SAMHSA) website, University of Maryland Center for Substance Abuse Research (CESAR) website,[35] Micromedex, and Lexicomp. No language limits were applied.

Results were uploaded into Covidence,[36] and following the removal of duplicates, titles and abstracts were screened independently by 2 reviewers. Data was extracted on gabapentin misuse, and abuse.

(1) In order to determine the nature of the problem, its magnitude and who is best placed to deal with the problem. Information was extracted on (a) prevalence of gabapentin misuse or abuse, (b) sources of gabapentin in the context of misuse/abuse, (c) drug effect sought/reason for abuse, (d) toxic/clinical presentation, and (d) overdoses.

(2) Information was also collected to help inform intervention strategies for who to target and potentially to review problem doses and consider dosage restrictions if appropriate including (a) populations at increased risk for misuse or abuse, (b) doses needed for abuse-related effects, and (c) factors increasing the abuse effect or risk for overdose/death.

(3) In order to determine the implications of lack of or failed interventions (to prevent abuse and adverse consequences), information was collected on management of intoxication, and about the cost associated with overdose (eg, hospitalizations).

We searched Pubmed for any studies in Utah about gabapentin misuse or abuse.

Human exposures to gabapentin reported to the Utah Poison Control Center between January 1, 2014 and September 30, 2019 were reviewed and a summary of cases were presented if the exposure involved gabapentin in patients of all ages, and for any reason for exposure.

Utilization data in the Utah Medicaid population was extracted.

Gabapentin pharmacokinetics (vs pregabalin)

Gabapentin has unpredictable pharmacokinetics and non-linear bioavailability.[9,37] Its systemic absorption is slow (peak plasma level within 3-4 hours)[38] and has low bioavailability (25-50%) compared to pregabalin (≥90%).[37] Gabapentin bioavailability varies by the dose administered e.g., 68% after a 300 mg dose vs 36% after a 1600 mg dose.[10,27,39] Because of pregabalin's quicker absorption, higher potency by 2.5-6 times higher, faster onset of action, faster plasma peak concentration by 3-fold, and higher bioavailability (>90%), it may be preferred for abuse purposes over gabapentin and may be more addictive..[10,26,27,37-40] A review of the European Medicines Agency (EMA) EudraVigilance (EV) database over the last decade showed more misuse-related adverse events for pregabalin compared to gabapentin.[26,41] Schifano et al state this confirms pregabalin's higher addictive liability.[14,26,41] Likewise, Bonnet and Scherbaum reached similar conclusions given pregabalin use was more frequently associated with behavioral dependence, and switches from prescription to self-administration.[14] Medications that slow gastrointestinal motility prolong the transit time of gabapentin in the small intestine and could potentially enhance the absorption and bioavailability of gabapentin.[37] In one study bioavailability increased by 50% when a 600 mg gabapentin dose was coadministered with oral morphine.[37,42] Gabapentin is excreted renally, without hepatic metabolism and with an excretion half-life of approximately 6 hours.[38]

Gabapentin enacarbil is a prodrug of gabapentin (hydrolyzed primarily in the intestines to gabapentin).[43] Gabapentin enacarbil (Horizant) and other gabapentin products are not interchangeable due to differences in formulation and pharmacokinetics and differences in approved indications.[43,44]

Gabapentin dosage

Appendix 1 contains dosage information for gabapentin, including maximum daily doses, with respect to indications, based on the FDA prescribing information and clinical guidelines. However, the effects and experiences of users (e.g. euphoria, increased energy, sedation, and dissociation) are more likely at higher doses, but can occur at any dose.[9]

Doses above 3600 mg/day regardless of indication appear inappropriate (See Table 1 of Appendix 1). There is a limited evidence to suggest therapeutic benefit from doses >3600mg for any indication (off-label included) of gabapentin. Higher doses are associated with more adverse effects (nausea,

somnolence) and abuse or misuse.[10] Since gabapentin has also been abused even at therapeutic doses, it is important to identify other potential indicators of abuse or misuse such as a pattern of very early refills (eg. more than 5 days before the previous supply runs out) and diagnoses for drug abuse.

Pediatric patients and patients with renal impairment require lower doses.[12]

Safety

Serious adverse effects with gabapentin include dizziness, somnolence, psychiatric reactions (thought disorder and disturbances, hostile behavior hyperactive behavior, mood swings, and suicidal thoughts) and others like immunologic reactions, hypoglycemia, and angioedema. Other common adverse effects include peripheral edema, ataxia (incoordination), fatigue and nystagmus (involuntary rapid eye movement).[8,45]

Reports and studies are emerging indicating that gabapentin, similar to pregabalin, is associated with effects often sought by drug abusers including sedative and/or psychedelic effects.[8]

Dose reductions are required in patients with renal insufficiency. Gabapentin is pregnancy risk factor C. It is present in breast milk and the risk versus benefit should be considered. Pregnancy registry outcome data following use during pregnancy and/or breastfeeding information is limited.[12,43]

In general, concomitant use of gabapentin with opioids and benzodiazepines or other CNS depressants should be avoided when possible, because of the risk of additive toxicity (adverse/toxic effects). These agents should only be combined if alternative treatment options are inadequate, and if combined, dosages and duration of each drug should be limited. Alcohol should be avoided with the use of the long-acting formulation, because the rate of absorption may be enhanced (increased release of drug).[43]

Centers for Disease Control and Prevention (CDC)

National Vital Statistics Reports: Regional Differences in the Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2017

It is important to consider the following information in the context of the limitations reported by the authors which included jurisdiction and time variations in death investigations and reporting practices, or medicolegal death investigation systems. This includes whether toxicological laboratory testing is performed to determine the type(s) of drugs present, substances tested for and the circumstances under which the tests are performed, resource factors (office staffing and personnel, caseload, budget, and availability of specific toxicology tests), interpretation of findings, potential misattribution of drugs, and decisions about which drugs to report on death certificates. The authors state that routine toxicological analysis can range from no testing at all, to urine screening with no further confirmation, to complete quantification of all potential toxins involved. Medical certifiers may include a single lethal drug and not multiple drugs involved or they may not want to impose an order when listing drugs.[46] Nevertheless, at least one drug or drug class was reported on the death certificate for 87.6% of drug overdose deaths in 2017, but this varied by region, nationally, between 75.4% and 98.9%.[46] The authors did conduct an adjustment analysis, and cautioned readers to consider the variation in the specificity of drug reporting by region when reviewing the results.[46] Also, multiple drugs are frequently involved in

overdose deaths and the authors state that the contribution of each drug to the death cannot be determined from the literal text analysis; this limitation should be considered.[4,5,46]

Gabapentin was amongst the top 15 drugs most frequently involved in drug overdose deaths in the United States in 2017; however, its involvement is much lower compared to other drugs such as fentanyl, heroin, cocaine, and methamphetamine.[46] Nationally in 2017, 2.6% of drug overdose deaths involved gabapentin compared to 38.9% involving fentanyl, 22.8% heroin, 21.3% cocaine, and 13.3% methamphetamine, and 6.9%–9.5% alprazolam, oxycodone, and morphine (each). The national age-adjusted rate, where gabapentin was found in persons with overdose, was 0.6 per 100,000 standard population; for region 8, with Utah, the age-adjusted rate was 1.6 per 100,000. Similarly methadone, hydrocodone, diphenhydramine, clonazepam, diazepam, amphetamine, and tramadol were each involved in less than 5.0% of drug overdose deaths.[46] Fentanyl remains the drug most frequently involved in drug overdose deaths in the United States (27,299/70,237= 39% of overdose deaths; age-adjusted rate of 8.7 per 100,000 vs. 29% in 2016; age-adjusted death rate of 5.9 per 100,000).[46]

Table A. Drugs most frequently involved in drug overdose deaths: United States, 2017

		United States (n = 70,237, 21.7)[1]		
Rank[2]	Referent drug group	Number of deaths	Percent[3]	Age-adjusted rate[4]
1	Fentanyl	27,299	38.9	8.7
2	Heroin	15,982	22.8	5.0
3	Cocaine	14,948	21.3	4.6
4	Methamphetamine	9,356	13.3	2.9
5	Alprazolam	6,647	9.5	2.1
6	Oxycodone	6,053	8.6	1.8
7	Morphine	4,874	6.9	1.5
8	Methadone	3,286	4.7	1.0
9	Hydrocodone	3,072	4.4	0.9
10	Diphenhydramine	2,286	3.3	0.7
11	Clonazepam	2,055	2.9	0.6
12	Diazepam	2,025	2.9	0.6
13	Gabapentin	1,848	2.6	0.6
14	Amphetamine	1,581	2.3	0.5
15	Tramadol	1,333	1.9	0.4

[1]Number and age-adjusted rate (deaths per 100,000 standard population) for all drug overdose deaths. Age-adjusted death rates were calculated using the direct method and adjusted to the 2000 standard population.
[2]Drugs were ranked by number of deaths. Ranks were not tested for statistical significance.
[3]Percentage of drug overdose deaths that involve the referent drug group.
[4]Age-adjusted death rates (deaths per 100,000 standard population) were calculated using the direct method and adjusted to the 2000 standard population.

NOTES: Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent drug group. Deaths involving more than one referent drug group (e.g., a death involving both heroin and cocaine) were counted in both totals. To avoid counting the same death multiple times, the numbers for drug-specific deaths should not be summated.

SOURCE: NCHS National Vital Statistics System, Mortality files linked with death certificate literal text, 2017.

Direct excerpt from report[46]

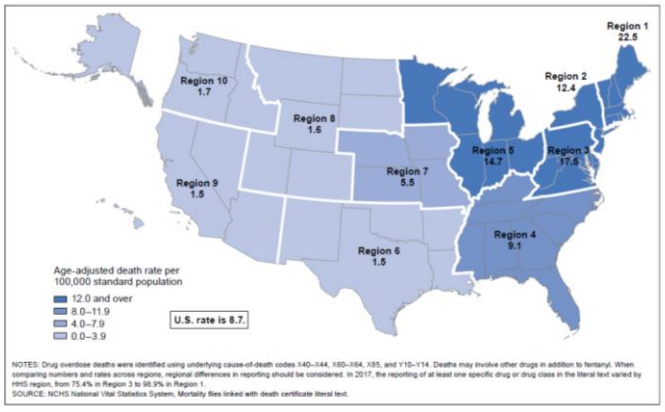


Figure 2. Age-adjusted rate of drug overdose deaths involving fentanyl, by region: 2017

Direct excerpt from report[46]

Gabapentin ranked among the top 10 most frequent drugs involved in drug overdose deaths in only one region (region 4). The top 10 most frequent drugs involved in drug overdose deaths in region 8 (Utah's region) are shown in table B below, from the report In Utah's region, the drug most commonly identified in overdose deaths was methamphetamine (28.7%), followed by heroin (21.2%) and oxycodone (16.2%). Gabapentin was not among the top 10 drugs identified among drug overdose deaths in region 8.

Region 8[1]— CO, MT, ND, SD, UT, and WY

Rank[2]	Referent drug group	Number of deaths	Percent[3]	Age-adjusted rate[4]
...	All drugs	1,994	100.0	16.7
1	Methamphetamine	572	28.7	4.9
2	Heroin	423	21.2	3.6
3	Oxycodone	324	16.2	2.7
4	Morphine	204	10.2	1.7
5	Cocaine	187	9.4	1.6
6	Fentanyl	185	9.3	1.6
7	Alprazolam	164	8.2	1.4
8	Diphenhydramine	129	6.5	1.1
9	Methadone	117	5.9	1.0
10	Hydrocodone	113	5.7	0.9

Direct excerpt from Table B of the report.[46]

Utah Poison Control Center (UPCC)

Utah Poison Control Center (UPCC) is one of 55 poison control centers serving the US (330 million people).[47] Appendix 4 contains a summary of cases over the last 5 years involving gabapentin from the UPCC. There were a total of 2,011 cases that involved gabapentin between January 1, 2014 and September 30, 2019, which is about 1% of the total UPCC human exposures. Almost two thirds of the gabapentin cases (62.2%) were due to intentional ingestion. The percentage gabapentin contributed to the total intentional exposures has increased from 3.2% in 2014 to 4.5% in 2019 (data for 2019 only until September 30). Intentional abuse and misuse overall constituted a small portion of the intentional cases (3.5% and 5.6% respectively) with suicide being the main category of intentional cases (50.4%). Suicide attempt as a reason for gabapentin exposure was documented in children as young as 6-12 years of age. It was the reason for the majority of cases in the 13-19 years of age category, as well as the most common intentional cause in adults. The majority of exposures were in adults (≥20 years of age; 80.71%) and there were slightly more female exposures (59.32%). Exposures in children ≤5 years of age accounted for approximately 10% of cases.

Of the total gabapentin exposures, most exposures (89.9%) occurred at a residence and slightly more than half of consults originated from a healthcare facility. Slightly more than two thirds of all exposures (68.3%) were managed in a healthcare facility with 22.8% treated and released from emergency departments, 15.6% admitted to critical care units, 10.5% to a noncritical care unit, and 15.5% to a psychiatric facility. Over the last 5 years, there were 91 (4.5% of the total gabapentin exposures) major effect outcomes and 3 deaths (0.2% of the total gabapentin exposures). Several other substances were documented concomitantly in gabapentin case records including ethanol, analgesics, anticonvulsants, antidepressants, antihistamines, cardiovascular drugs, muscle relaxants, hormones, sedative hypnotics/antipsychotic agents, and stimulants/street drugs. Documentation of analgesics, antidepressants, and sedative hypnotics/antipsychotic agents appear more frequently (please refer to appendix 4 for additional information).

Drug Abuse Warning Network (DAWN)

Until 2011, DAWN produced estimates of drug-related emergency department visits.[48] ED visit rates (per 100,000 population) for gabapentin increased from 2.7 in 2004 to 4.9 in 2011.[8] SAMHSA is re-establishing the DAWN surveillance system on a smaller scale with improved timeliness of data ('early warning' system) and data abstraction will begin in mid-2019.[48]

Factors that may increase risk of adverse events/abuse

- **Patients with a history of substance abuse:** A history of or current drug abuse, particularly opioids, appears to be a risk factor for gabapentin misuse.[9]
- **High doses:** Doses exceeding recommended doses increase the risk of adverse events without offering any additional treatment benefit. Appendix 1 contains dosage information on gabapentin by indication, based on the FDA prescribing information and clinical guidelines. The majority of case reports of misused gabapentin involved prescribed gabapentin where patients took higher doses than prescribed doses.[9] Unlike some other drugs of abuse, users develop tolerance to the euphoric high of gabapentin[14] which is "…suggested to drive a considerable overdosing."[14,49,50] Bonnet and Scherbaum state that that the toxicity profile of gabapentinoids is controversial.[14]
- **Extended treatment periods/ Long-term use:** Long-term use could lead to dependence, withdrawal on discontinuation, and a prolonged risk for adverse events including dangerous drug interactions (i.e., CNS depression with opioids). Nonetheless, the benefits may outweigh these risks for many patients. It may also increase the amount of gabapentin available for diversion and abuse.
- **Concomitant opioid and gabapentin:** Gomes et al (large study; >16 years) found a substantial increase (49%) in the risk of opioid-related death in patients receiving concomitant opioid and gabapentin treatment.[51] Also, moderate (900 to 1,799 mg daily) or high dose (1,800 mg daily or more) was associated with a nearly 60% increased odds of opioid-related death compared to exposure to opioids alone (secondary analysis), and a very high dose (2,500 mg daily or more) of gabapentin was associated with a nearly 2-fold increased odds of opioid-related death (post-hoc analysis). Low gabapentin dose (<900 mg daily), was not significantly associated with an increased odds of opioid-related death.[51]
- **Multiple CNS drugs** e.g. patients using more than one drug causing CNS depression.
- Patients whose job or lifestyle requires unimpaired intellectual or psychomotor function

Off-label use

Gabapentin is being used off-label for a variety of conditions (estimated to be 83-95% if its use), some which have supportive evidence and are recommended by clinical practice guidelines. Nonetheless, because its exact mechanism is unclear and the medication in the past had been regarded as having no abuse potential (ie, non-controlled status), prescribing rates may have expanded more rapidly compared to if the drug was regarded as a controlled substance with abuse potential.[9,52,53] There is insufficient evidence or no current evidence to support the use of gabapentin as treatment in patients with substance use disorder (misuse/abuse/dependence other than alcohol).[13,54-62] Off-label uses of gabapentin supported by guidelines include the following:

- moderate to severe alcohol use disorder (APA[63] and VADoD[64]; level B evidence)

- alternative agent for alcohol withdrawal when the risk of benzodiazepines outweigh the benefit (VADoD[64]; level B evidence)
- alternative agent for chronic refractory cough (ACCP[65]; level C evidence),
- neuropathic pain other than postherpetic neuralgia (ie, peripheral neuropathy, diabetic neuropathy (IASP,[66] EFNS,[67] SCCM,[68] NICE,[69] AAN,[70] ADA[71]; level A evidence),
- postoperative pain as part of a perioperative multimodal analgesia regimen to decrease postoperative pain and opioid use (American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council;[72] level B),
- chronic pruritus of neuropathic origin or malignancy related, and uremic pruritis (chronic kidney disease-associated pruritus) (European Dermatology Forum (EDF) and European Academy of Dermatology and Venerology (EADV) guidelines;[73] level C and B, respectively),
- alternative for vasomotor symptoms (hot flashes) in postmenopausal women and breast cancer survivors (American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) position statement on menopause,[74] the Endocrine Society (ES) guideline on treatment of symptoms of menopause,[75] and the North American Menopause Society (NAMS) position statement on nonhormonal management of menopause-associated vasomotor symptoms,[76] American Cancer Society/American Society of Clinical Oncology (ACS/ASCO) breast cancer survivorship care guideline;[77] level B),
- restless leg syndrome (gabapentin enacarbil is FDA-approved for this indication) (The American Academy of Sleep Medicine (AASM) guidelines regarding RLS management,[78] The European Federation of Neurological Societies/European Neurological Society/European Sleep Research Society (EFNS/ENS/ESRS) Task Force guidelines,[79] the International Restless Legs Syndrome Study Group, European Restless Legs Syndrome Study Group, and RLS Foundation (IRLSSG/EURLSSG/RLS-F) guidelines for the prevention and treatment of dopaminergic augmentation in restless legs syndrome;[80] level B).[12]

Because restless legs syndrome (RLS)/Willis-Ekbom disease (WED) is common during pregnancy (affecting approximately one in five pregnant women), a task force chosen by the International RLS Study Group (IRLSSG) developed guidelines for the diagnosis and treatment of RLS/WED during pregnancy and lactation.[81] These guidelines state that there is insufficient evidence to recommend gabapentin use in pregnant women for restless leg syndrome (off-label use), and that gabapentin may be considered for the treatment of refractory restless leg syndrome in breastfeeding women (Picchietti 2015).[12,43] Even though gabapentin may be used for moderate to severe alcohol use disorder in certain situations (APA[63] and VADoD[64]; level B evidence), APA guidelines state that pharmacological agents should not be used for the treatment of alcohol use disorder in pregnant or breastfeeding women unless needed for the treatment of acute alcohol withdrawal or a coexisting disorder.[12,43,63,81]

Off-label uses in Lexicomp without guideline recommendations (may need additional evidence) include fibromyalgia (level B), persistent or intractable hiccups (singultus) (level C), and social anxiety disorder as an adjunct to antidepressants or monotherapy (alternative agent) (level C).[12]

Please refer to guidelines for details and specifics of recommendations.

Definitions of levels of evidence:
"A - Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form (eg, results of the introduction of penicillin treatment) to support the off-label use. Further research is unlikely to change confidence in the estimate of benefit.
B - Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.
C - Evidence from observational studies (eg, retrospective case series/reports providing significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials (eg, when limited options exist for condition). Any estimate of effect is uncertain.
G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline."[43]

Systematic reviews of abuse or misuse

Appendix 3 contains evidence from the included systematic reviews.

In the general population the prevalence of gabapentin abuse appears low (~1%). Current or past substance abusers particularly opioids (15-22%), but also benzodiazepine, cocaine, cannabis, heroin, and other illicit drug users, appear to be at increased risk for gabapentin abuse. Other populations at increased risk for misuse or abuse of gabapentin include patients with psychiatric comorbidities, patients that are suicidal, patients that are vulnerable to the increased 'pro-drug' information on the web like children/adolescents, and inmates. More patients prescribed gabapentin abuse it compared to those without a prescription. Prescriptions appear to be a major source of the abused/misused gabapentin. Reasons for abuse include to "get high" (whilst producing only few side-effects), to potentiate methadone high or buprenorphine/naloxone effect, to avoid detection during urine drug screening, used as a cutting agent for heroin, substitute for cocaine, to alleviate opioid withdrawal symptoms, self-medication of uncontrolled pain, anxiety, or withdrawal of other drugs/minimize cravings, and intentional self-harm. Toxic effects include various such as CNS symptoms and psychedelic effects. It is controversial how toxic gabapentin is on its own. It is often taken in combination with other drugs. Overdoses, and data from post-mortem toxicology analyses have been included in table 1 (appendix 3). Doses needed for abuse-related effects include therapeutic doses, and supratherapeutic doses. Patients may be taking usual doses as a single dose so it may not always be evident from prescriptions when it is being misused. Factors increasing the abuse effect or risk for overdose/death include concurrent use with other drugs such as opioids and other CNS depressants, high doses, administration via other non-oral routes, and access because it is not controlled. Not much is reported in these systematic reviews for management of gabapentin intoxication, apart from the case reports. Some report that it is relatively safe even following acute overdose, that outcomes are generally mild-moderate, and resolved within 10 hours in case series. Outcomes may be more severe when taken with other drugs and with renal impairment. None of the systematic reviews included information on the cost associated with overdose.[9,10,14,38,49,82]

Bonnet and Scherbaum state that the assumption that gabapentinoids are being abused (because it if easily obtainable) corresponds to pharmacoepidemiological analyses of prescription data and spontaneous reports to pharmacovigilance databases (mainly Scandinavia, UK, and Germany).[14] However, they also note that it could just be that gabapentinoids are "innocent bystanders of other

more powerful substance use disorders (SUD)."[14] They reviewed the gabapentinoids' addiction risk and did not find sufficient evidence "of a vigorous addictive power of gabapentinoids" or for people seeking treatment for gabapentinoid use disorder. In patients without a prior abuse history, there were very few cases of dependence symptoms i.e. "wanting" (N=4) and these were for pregabalin and not gabapentin. Patients with current or past substance use disorders (mostly opioid and multi-drug users) appeared to be at risk for abuse of gabapentinoids. When taken on its own in overdose, gabapentinoids appeared safe, but the risk for lethal outcomes increased when taken with other drugs especially opioids and sedatives. The authors recommend "in patients with a history of SUD, gabapentinoids should be avoided or if indispensable, administered with caution by using a strict therapeutic and prescription monitoring."[14]

Limitations of current evidence include inherent bias of studies (study designs include retrospective reviews, survey data, and case reports), publication bias (more publications since the abuse issue received more attention), literature searches of the included systematic reviews were not comprehensive, inconsistent data reporting and insufficient description of the included studies of some systematic reviews, insufficient risk of bias assessment in the systematic reviews, lack of reporting of funding sources of included studies in systematic reviews, generalizability (e.g., to other countries), and combined reporting of gabapentin and pregabalin in some cases (effects may be different). [9,10,14,38,49,82]

Studies in Utah

No studies were identified for gabapentin misuse or abuse in Utah. The single study that was identified was excluded, because it was not about abuse or misuse. It describes an assay to support therapeutic drug monitoring of gabapentin and levetiracetam in plasma.[83]

Factors and limitations to consider

- **CDC:** In an effort to resolve the drug overdose epidemic, CDC developed and published the *CDC Guideline for Prescribing Opioids for Chronic Pain* (longer than 3 months or past the time of normal tissue healing; outside of active cancer treatment, palliative care, and end-of-life care) recommending nonpharmacologic therapy and nonopioid pharmacologic therapy as preferred for chronic pain, and that opioid therapy only be considered if "expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate (recommendation category: A, evidence type: 3)."[6]
- **Access:** Gabapentin is inexpensive (referred to among drug-users as 'a cheap man's high') and it is relatively easy to acquire by prescription.[9] Prescription gabapentin is the primary source of gabapentin misused in the United States and the United Kingdom.[9] However, it has been speculated that gabapentin (if assuming that gabapentin overdoses are less life-threatening than with other drugs) may be replacing more toxic other drugs like benzodiazepines on the prescriptions and black market.[14]
- **Dosage:** Gabapentin can be abused at any dose, but higher doses may be associated with abuse more than lower doses. (e.g., consider higher than therapeutic recommended dose of >3600 mg). Potential intervention strategies include limiting quantities prescribed and cumulative doses, identification of repeat supply issues (eg refill pattern), or education to help curb abuse and diversion.[10,26,84]

- **Indications:** Gabapentin is FDA-approved as adjunctive therapy in the treatment of epilepsy (partial onset seizures, with and without secondary generalization) in patients >3 years old, for the treatment of post-herpetic neuralgia in adults, and restless leg syndrome (extended-release).[11] Other uses are off-label; however, several off-label uses of gabapentin have supportive evidence and/or clinical guidelines recommending gabapentin as a treatment option (See off-label use section of the report).[12,13]
- **Concomitant gabapentin and opioid use: I**f gabapentin and opioids are used concurrently (combination use is believed to provide better pain relief in certain circumstances[85]), does the benefit outweigh the risk and is a consideration for lower doses of each agent assessed? Quintero states that gabapentin can interact synergistically with tramadol for alleviating pain.[38]
- **Special populations:** Gabapentin may be preferred in elderly patients, those with hepatic disease and those with cancer because of its pharmacokinetics (not hepatically metabolized) and limited drug interaction profile**.**[38,86,87]
- **Widely used mostly for off-label indications:** Educating prescribers to use caution when prescribing off-label and to consider referring patients to pain specialists who require gabapentin + opioid if necessary for appropriate pain management.[10,84]
- **Misuse or abuse/inappropriate use (potential indicators):** Behaviors that could indicate misuse include exaggeration of symptoms, requesting specific drugs or higher doses during appointments, doctor shopping or receiving prescriptions for the same medication from multiple prescribers who are at different practice locations, claiming medications were lost or stolen, filling prescriptions at multiple pharmacies, fabrication of prescriptions, requesting not to bill insurance and instead paying out-of-pocket for medications, or requesting very early refills from the pharmacy (>6 days before supply runs out.[9,10,88,89]
- **Patient experience evidence:** Views and real-world user experience of patients are important because these are rarely captured in conventional randomized-controlled trials.[82] The development of tools to capture the experiences of Utah Medicaid patients and prescribers regarding treatment options, monitoring of progress during treatment, and support services available or that they are unaware of may be useful. Marsden et al found that "patients reported that withdrawal symptoms might not be well understood by prescribers, so improved training and guidance for clinicians are required."[82]
- **Urine drug screening (UDS):** A negative drug screen for a prescribed medication may indicate diversion. It has been suggested to add gabapentinoids to standard UDS,[10,90] but it has not yet been included. It may be useful in patients at high risk of abuse such as those with substance use disorders given that some patients specifically abuse gabapentinoids because it is not detected on routine UDS.[10,88,90,91]
- **High risk populations for abuse:** Patients with current or past substance use disorder (particularly opioids). Other populations at increased risk for misuse or abuse of gabapentin include patients with psychiatric comorbidities, patients that are suicidal, patients that are vulnerable to the increased 'pro-drug' information on the web like children/adolescents, and inmates.[9,10,14,38,49,82]
- **Deprivation:** Marsden et al in a national mixed-methods study in England found a strong and increasing association between gabapentinoids, opioids, and antidepressants and deprivation. Deprivation was measured by English Indices of Multiple Deprivation (IMD) which is a weighted combination of 37 indicators of income, employment, education, skills and training, health and disability, crime, barriers to housing and services, and living environment. They also state that the "association with increasing deprivation is reflected in the association between chronic pain and unemployment."[82,92]

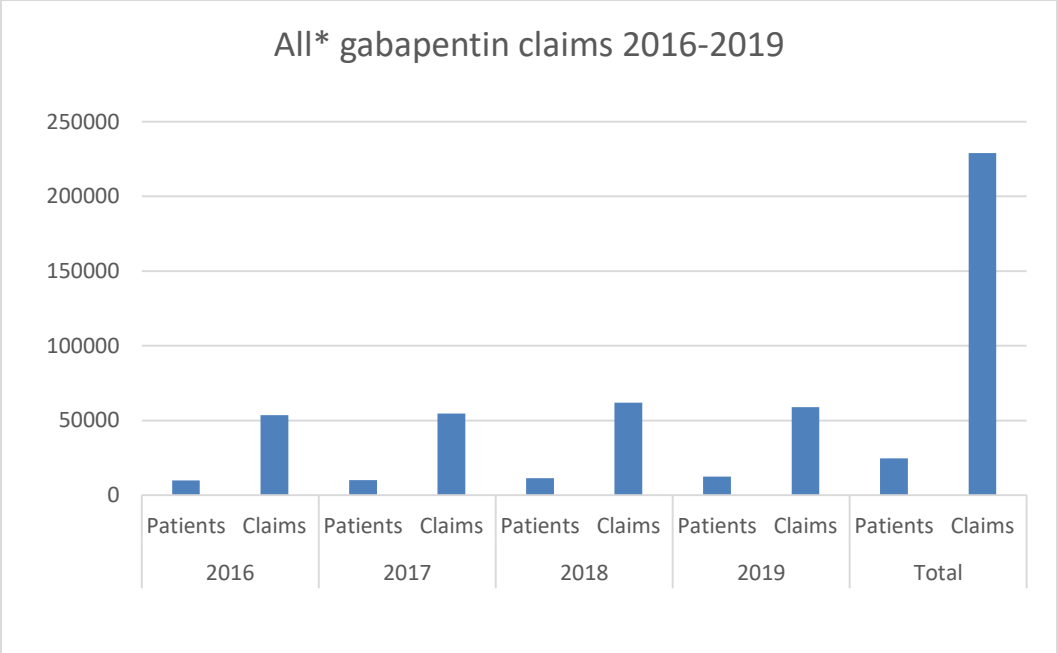
- **Consider consultation with behavioral health service experts/referring patients** with complex conditions e.g. current or history of alcohol or drug use disorder, or concurrent severe psychiatric disorder
- **Long-term use:** Marsden et al report that public health guidance in England for prescribers on gabapentinoids focuses on avoiding risks of misuse and dependence, without stipulating any limit on duration of treatment.[82,93] In March 2018, an estimated 53% of people in England that had prescriptions for gabapentinoids received it long-term (>12 month). The authors of the mixed-method public health review and database study state that whilst it may be appropriate for those with epilepsy to take it long-term, patients being treated for other conditions may be dependent and need support to discontinue taking gabapentinoids.[82] The authors state that it is important to ensure that restrictions do not cause unintended negative consequences (ensuring patients can benefit from treatment where needed).[82]
  Bonnet and Scherbaum (2017) did not find any case reports about gabapentin self-administration for longer than one year.[14] The only longitudinal study found and described in their paper, is a prospective study in adults using non-medical prescription opioids in Apalachian Kentucky (n=503; self-report questionnaire of psychoactive substances).[94] The authors of the systematic review report that this study found a considerable increase of gabapentin misuse in this population within 5 years.[14,94]

Utah Medicaid Utilization Data

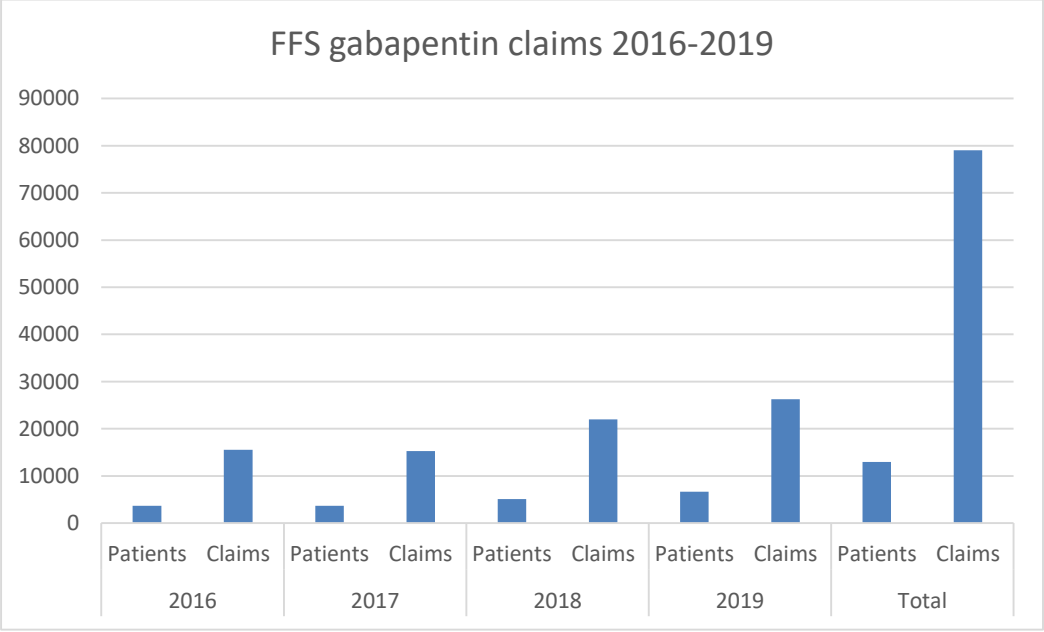
ALL refers to all Medicaid patients including Fee for Service and Accountable Care Organization (ACO) patients. FFS refers to Fee for Service only patients.

A. Overall total utilization of gabapentin (2016-2019)

Please refer to Appendix 5 for additional information.

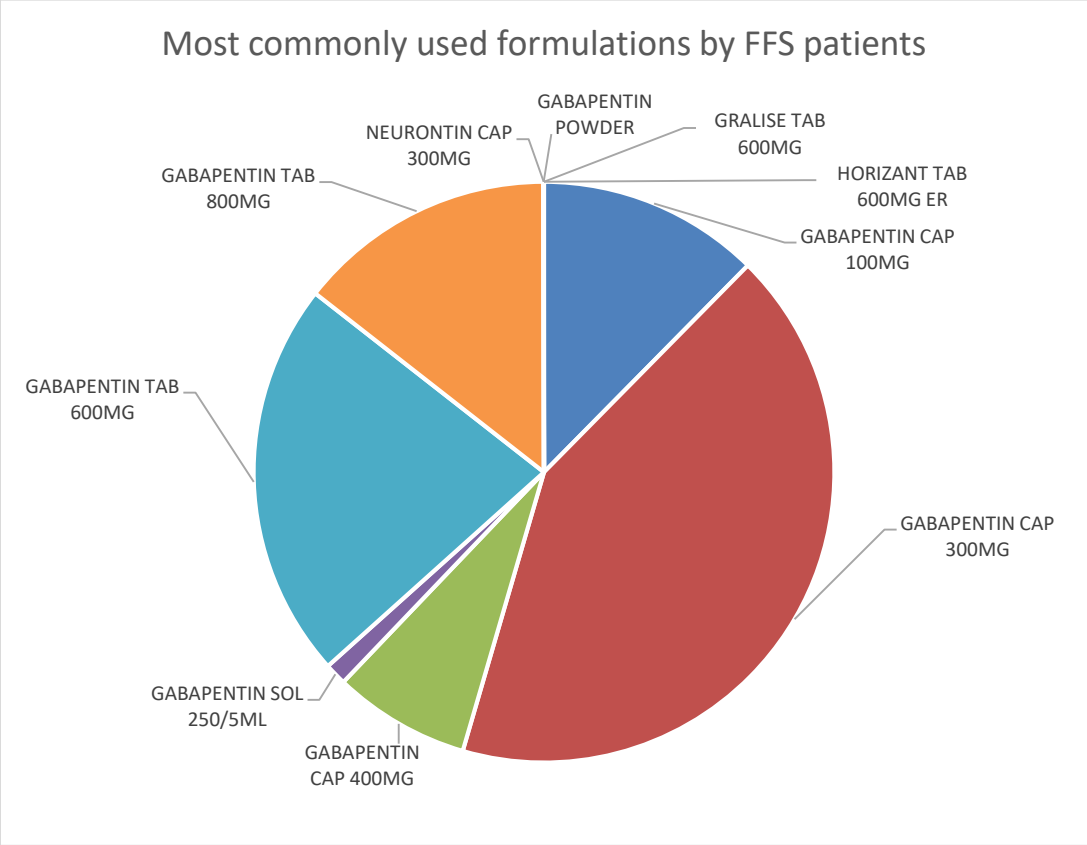


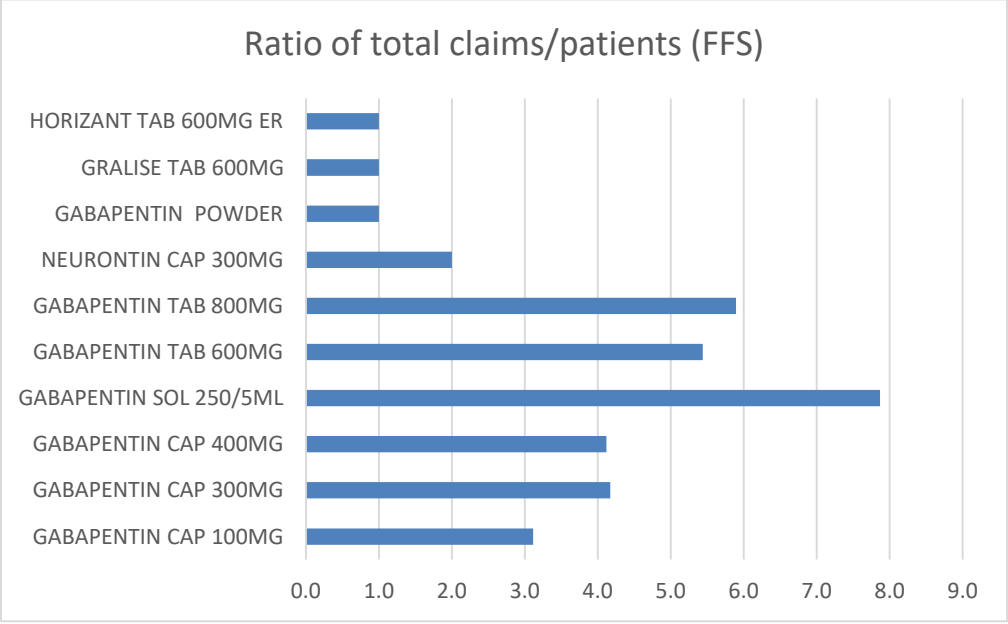
*FFS and ACO



- The number of patients and claims for gabapentin appears to be increasing in the FFS population. This may be related to efforts to reduce opioid use.

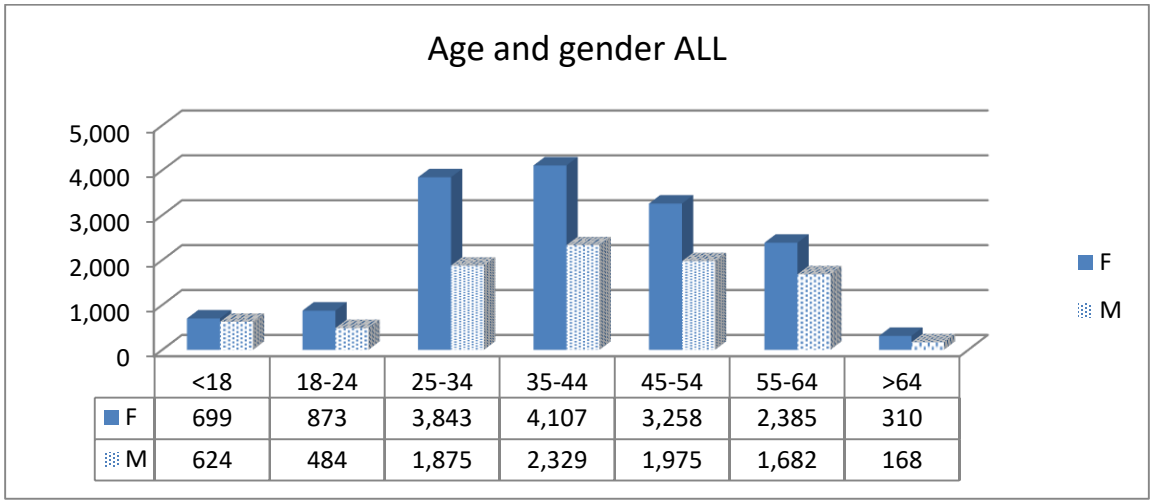
B. Most commonly used gabapentin formulations (2016-2019)



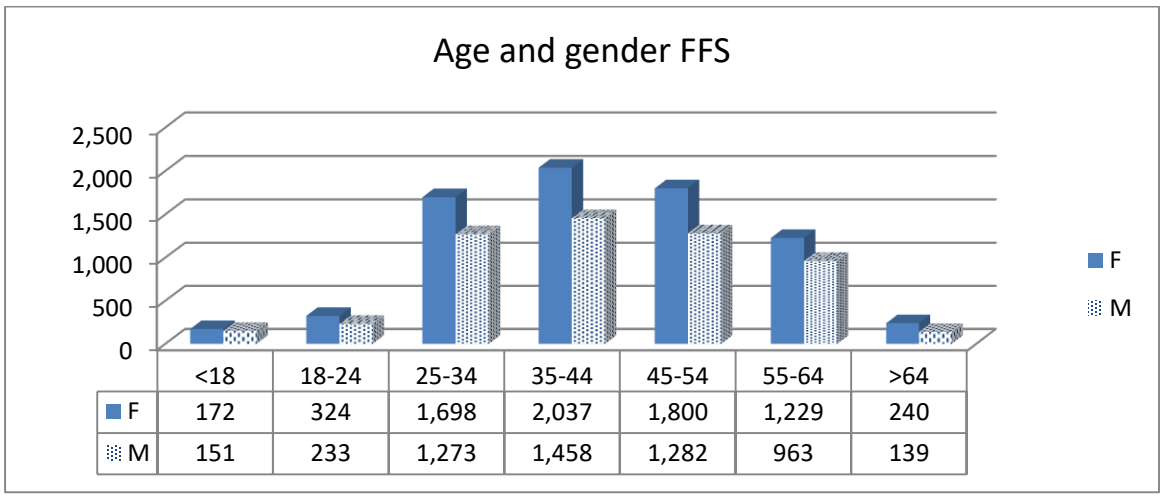


Whilst the pie chart shows the most commonly used formulations, the ratio demonstrated that the liquid formulation is associated with the mot claims per patient. This may reflect pediatric patients and those in care facilities and the flexibility of oral formulations.

C. Age and gender (2016-2019) for ALL and FFS groups



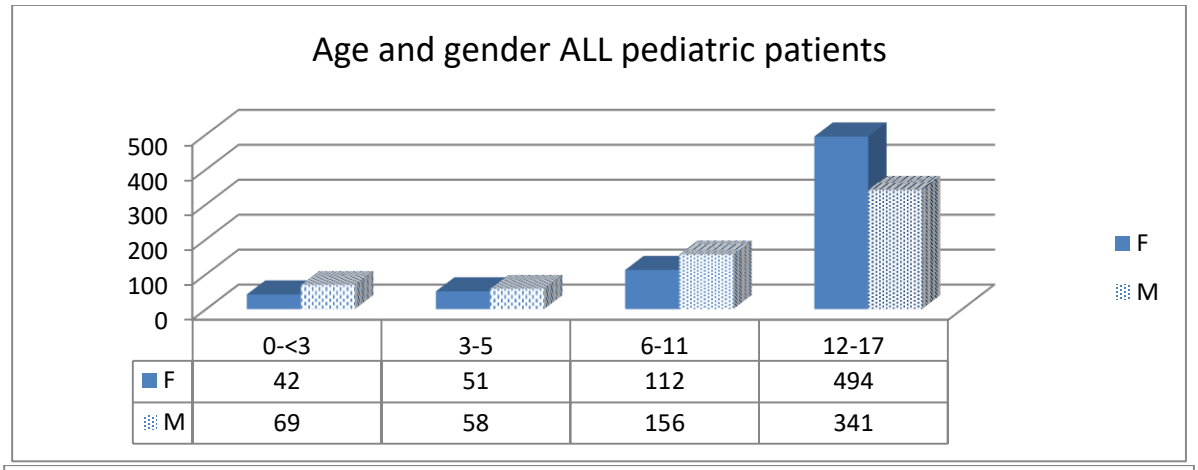
	<18	18-24	25-34	35-44	45-54	55-64	>64
F	699	873	3,843	4,107	3,258	2,385	310
M	624	484	1,875	2,329	1,975	1,682	168

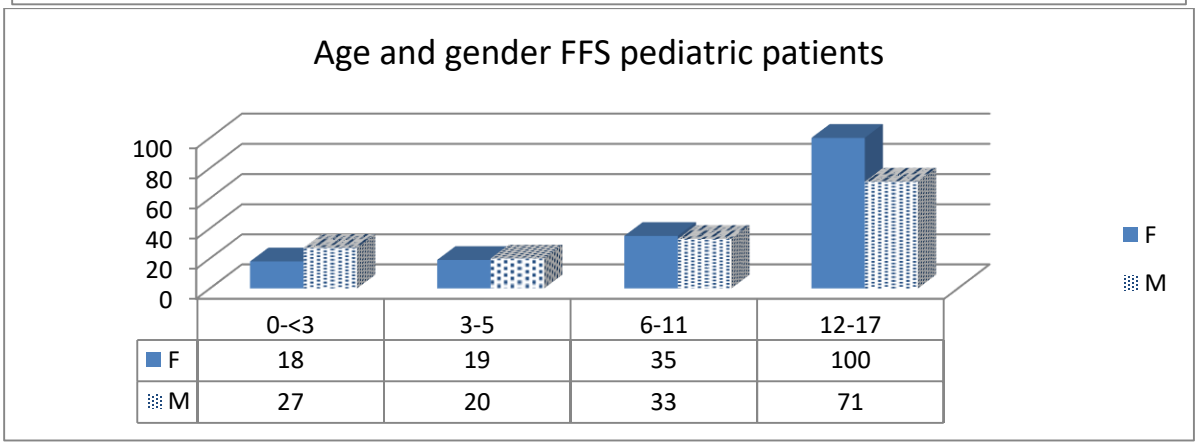


	<18	18-24	25-34	35-44	45-54	55-64	>64
F	172	324	1,698	2,037	1,800	1,229	240
M	151	233	1,273	1,458	1,282	963	139

Age group	% of total FFS (12999)	% of total ALL (24612)
<18	2.48%	5.38%
18-24	4.28%	5.51%
25-34	22.86%	23.23%
35-44	26.89%	26.15%
45-54	23.71%	21.26%
55-64	16.86%	16.52%
65+	2.92%	1.94%

- The distribution of gabapentin use by age groups appear similar between ALL and FFS patients.





Age group	% of total ped FFS (323)	% of total ped ALL (1323)
0-<3	13.93%	8.39%
3-5	12.07%	8.24%
6-11	21.05%	20.26%
12-17	52.94%	63.11%

- It appears more FFS pediatric patients in the 0-<3 and 3-5 years old groups are receiving gabapentin compared to ALL pediatric patients, and fewer in the 12-17 year old group.

D. Diagnoses (FFS all age groups)

How many patients had diagnosis codes submitted for the following?
However, it is important to consider that there are several limitations when reviewing data based on diagnosis codes.

Diagnosis grouping	Number of FFS patients with diagnosis code of interest submitted	Percentage of total FFS patients that received gabapentin (2016-2019) (n=12,999)
A EPILEPSY/SEIZURES	1,421	10.93%
N POSTHERPETIC NEURALGIA	21	0.16%
R RESTLESS LEGS SYNDROME	521	4.01%
B ALCOHOL MISUSE	1,831	14.09%
C DRUG DEPENDENCE	3,752	28.86%
D DRUG ABUSE	2,966	22.82%
E POISONING (any substance)	734	5.65%
G ACCIDENTAL POISONING (subset of poisoning)	631	4.85%

- More than a fifth of patients had a diagnosis code submitted (2016-2019) for drug abuse (this population may be at increased risk for abusing gabapentin).

E. Pediatric patients

- A total of 323 pediatric FFS patients under 3 years of age have received prescriptions for gabapentin although it is only FDA-approved as adjunctive therapy in the treatment of epilepsy in pediatric patients >3 years old.[12,13]

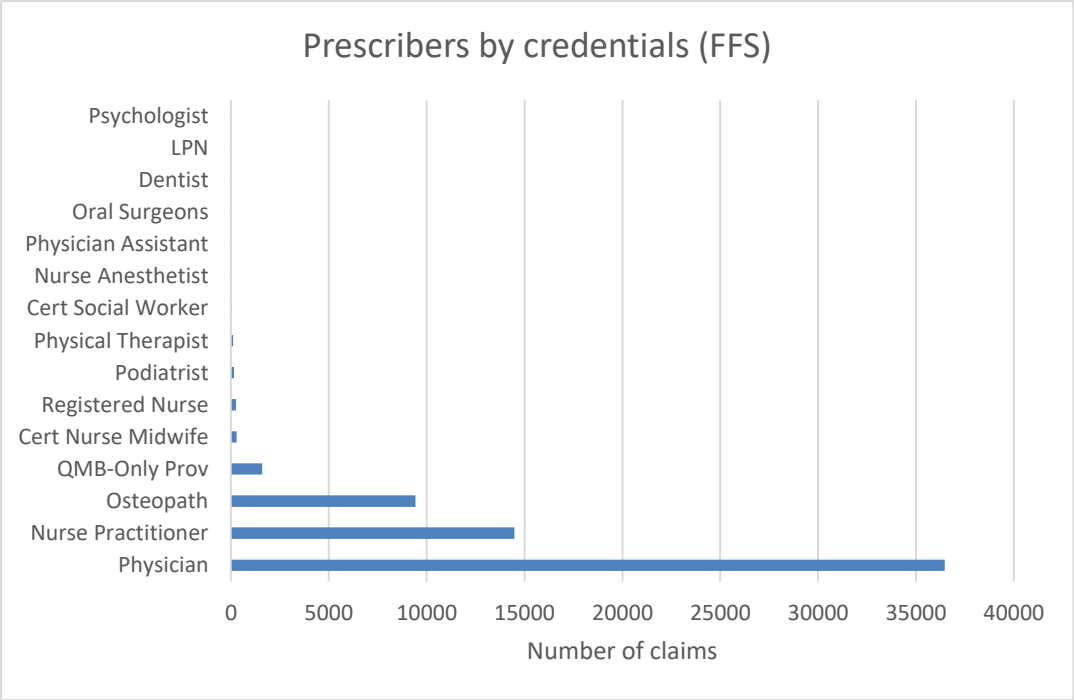
Diagnosis	Number of FFS pediatric patients with diagnosis code of interest submitted (2016-2019)	Percentage of total FFS pediatric patients that received gabapentin (2016-2019) (n=323)
A EPILEPSY	101	31.27%
N POSTHERPETIC NEURALGIA	0	0%
R RESTLESS LEGS SYNDROME	6	1.9%
B ALCOHOL MISUSE	10	3.10%
C DRUG DEPENDENCE	19	5.88%
D DRUG ABUSE	27	8.36%
E POISONING (any substance)	14	4.33%
G ACCIDENTAL POISONING (subset of poisoning)	9	2.79%

Additional information on diagnosis codes submitted in these patients have been included in appendix 5 (table 4), with select information summarized below.

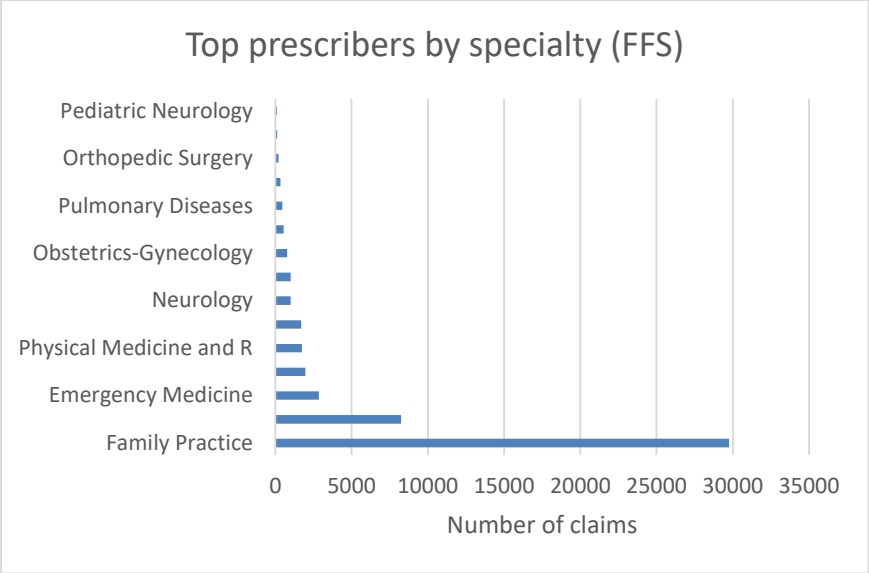
- 33-67% of the FFS pediatric patients in each age group under 9 years old had a diagnosis code for epilepsy, and 5-60% of those 10-17 years old. This suggests lack of diagnosis code submission or off-label, perhaps inappropriate use of gabapentin.
- None of the pediatric patients had a diagnosis for postherpetic neuralgia.
- 3-15% of the FFS pediatric patients in each age group 15-17 years old had a diagnosis for alcohol misuse (none of the remaining pediatric patients had this diagnosis).
- 6/19 patients that had a diagnosis submitted for drug dependence were under 3 years old; the majority were 15-17 years old. For the youngest patients this may reflect maternal drug abuse.
- Patients with a diagnosis for drug abuse were 11-17 years old; the majority were 14-17 years old (5-29% of patients of this age). Gabapentin misuse/abuse may be likely (if drug abuse is a risk factor for gabapentin abuse/misuse) in these patients.
- Patients with a diagnosis for poisoning or accidental poisoning were 9-17 years old.

F. Prescribers of gabapentin (FFS)

Note that provider information may not be complete and some prescribers have multiple specialties or credentials.



FFS Credentials		FFS Credentials	
Credentials	RXs	Credentials	RXs
Physician	36476	Physician Assistant	5
Nurse Practitioner	14480	Oral Surgeons	4
Osteopath	9423	Dentist	3
QMB-Only Prov	1587	LPN	1
Cert Nurse Midwife	285	Psychologist	1
Registered Nurse	254	Unknown	17628
Podiatrist	162		
Physical Therapist	100		
Cert Social Worker	30		
Nurse Anesthetist	11		



Note that the prescriber assigned to a prescription may not be the originating provider, but rather the primary care provider who is continuing prescriptions written by other, perhaps specialist, providers.

G. Doses

Number of patients that received this daily dosage at any point during our timeframe (2016-2019)

All

Maximum single Rx dose

Dose*	**Number of patients**
>3600 mg	285
>2400-3600 mg	2831
>1800-2400 mg	3105
900-1800 mg	11924
300-<900 mg	5552
<300 mg	915

FFS

Dose*	**Number of patients**
>3600 mg	118
>2400-3600 mg	1576
>1800-2400 mg	1930
900-1800 mg	6379
300-<900 mg	2598
<300 mg	398

Maximum single Rx dose (excluding solutions)◊

Dose*	**Number of patients**
>3600 mg	282
>2400-3600 mg	2825
>1800-2400 mg	3094
900-1800 mg	11856
300-<900 mg	5358
<300 mg	737

Dose*	**Number of patients**
>3600 mg	116
>2400-3600 mg	1573
>1800-2400 mg	1921
900-1800 mg	6359
300-<900 mg	2536
<300 mg	332

*Used single prescription to calculate this: (Quantity/day supply) x strength of formulation; this is underestimating the number of patients because it does not capture dosing of patients that received multiple prescriptions overlapping/different strength formulations on separate prescription(s).

◊It was unclear whether the quantity in the claims data is the actual mL amount.

Prescribers of patients with >3600mg/day

Specialty ALL

Specialty	RXs
Family Practice	2826
Internal Medicine	851
Emergency Medicine	199
Physical Medicine and R	193
Anesthesiology	151
Psychiatry	126
Neurology	114
Obstetrics-Gynecology	48
Infectious Diseases	41
Pulmonary Diseases	33
Pediatrics	29
Child Psychiatry	20
Orthopedic Surgery	15
General Practice	8
Hematology	3
Oncology	3
Gastroenterology	2
General Preventive Medi	1
Otorhinolaryngology	1
Unknown	2845

Specialty FFS

Specialty	RXs
Family Practice	919
Internal Medicine	145
Emergency Medicine	82
Neurology	39
Physical Medicine and R	17
Child Psychiatry	15
Pulmonary Diseases	11
Psychiatry	10
General Practice	6
Anesthesiology	4
Obstetrics-Gynecology	3
Orthopedic Surgery	2
Infectious Diseases	1
Otorhinolaryngology	1
Unknown	530

ALL Credentials

Credentials	RXs
Physician	3328
Nurse Practitioner	1084
Osteopath	972
QMB-Only Prov	96
Registered Nurse	40
Cert Nurse Midwife	39
Physical Therapist	7
Cert Social Worker	4
LPN	2
Podiatrist	2
Psychologist	2
Physician Assistant	1
Unknown	1611

FFS Credentials

Credentials	RXs
Physician	717
Osteopath	446
Nurse Practitioner	206
QMB-Only Prov	17
Cert Nurse Midwife	9
Registered Nurse	9
Physical Therapist	7
Unknown	288

H. Long-term users (>12 months) (2016-2019)

Continuous use is defined as continuous days' supply for any gabapentin formulation. 30 days missing data/gap was regarded as ongoing. However, if there were >30 days in which there were no days' supply, we took this to indicate that continuous use had ended.

- Among ALL patients, 4645 are long-term users (4645/24612 x 100 = 18.9%).
- Among FFS patients, 1296 are long-term users (1296/12999 x 100 = 10%).

Prescribers of long-term gabapentin users are shown below.

ALL Credentials

Credentials	RXs
Physician	63454
Nurse Practitioner	23221
Osteopath	14275
QMB-Only Prov	4849
Podiatrist	346
Registered Nurse	343
Cert Nurse Midwife	297
Physical Therapist	73
Cert Social Worker	38
Group Practice	37
Psychologist	21
Physician Assistant	18
Dentist	12
Nurse Anesthetist	11
LPN	5
Oral Surgeons	3
Optometrist	1
Unknown	29995

FFS Credentials

Credentials	RXs
Physician	16449
Nurse Practitioner	4995
Osteopath	4734
QMB-Only Prov	600
Registered Nurse	116
Podiatrist	69
Cert Nurse Midwife	60
Physical Therapist	25
Nurse Anesthetist	9
Oral Surgeons	2
Cert Social Worker	1
Dentist	1
LPN	1
Unknown	6440

Specialty ALL

Specialty	RXs
Family Practice	44965
Internal Medicine	15096
Pediatrics	4366
Physical Medicine and R	3997
Psychiatry	3740
Neurology	3204
Emergency Medicine	3125
Anesthesiology	2207
General Practice	1046
Child Psychiatry	909
Obstetrics-Gynecology	825
Pulmonary Diseases	806
General Preventive Medi	553
Rheumatology	405
Infectious Diseases	279
Pediatric Neurology	256
Orthopedic Surgery	232

Specialty FFS

Specialty	RXs
Family Practice	14221
Internal Medicine	3878
Emergency Medicine	1324
Pediatrics	1136
Physical Medicine and R	926
General Practice	486
Psychiatry	370
Obstetrics-Gynecology	368
Neurology	344
Pulmonary Diseases	244
Anesthesiology	145
General Preventive Medi	113
Pediatric Neurology	80
Child Psychiatry	61
Orthopedic Surgery	29
Gastroenterology	26
Ophthalmology	23

Specialty ALL

Specialty	RXs
Oncology	202
Hematology	127
Gastroenterology	101
Nephrology	99
General Surgery	90
Endocrinology	86
Cardiology	83
Geriatrics	58
Neonatology	41
Ophthalmology	41
Pathology	41
Cardiovascular Diseases	31
Gynecology	29
Diagnostic Radiology	24
Neurological Surgery	22
Dermatology	21
Otorhinolaryngology	21
Radiation Oncology	21
Plastic Surgery	12
Neuroradiology	10
Neuropathology	8
Aerospace Medicine	7
Diabetes	7
Hand Surgery	7
Cardiovascular Surgery	4
Radiology	3
Urology	3
Pediatric Surgery	2
Colon and Rectal Surger	1
Unknown	58226

Specialty FFS

Specialty	RXs
Infectious Diseases	22
Hematology	21
Oncology	20
Nephrology	18
Rheumatology	10
Dermatology	7
Cardiology	6
Neurological Surgery	5
General Surgery	4
Pathology	4
Cardiovascular Diseases	3
Geriatrics	2
Colon and Rectal Surger	1
Otorhinolaryngology	1
Unknown	12277

I. Additional potential problematic use data

Appendix 6 contains information on:
(Table number as listed in appendix listed first e.g. T1)

T1+T3. The number of patients Number of patients (ALL+FFS) by number of prescriptions (in last year) with select diagnoses.

T2+T4. Number of patients (ALL+FFS) by number of prescriptions (in last year) that fulfil select criteria (>1 Gabapentin (within 30 days), 1 Pharmacy (within 30 days), >1 Prescriber (GABA/Opioid) within 30 days, >3600mg/day, >400 days' supply (year), concurrent pregabalin, concurrent opioid, concurrent benzodiazepine, concurrent opioid and benzo, concurrent "muscle relaxant", concurrent hypnotic, concurrent opioid+benzo+muscle relaxant+hypnotic)

- Patients that have more than 25 prescriptions in the 1-year period were reviewed briefly and they fall into 2 categories. Patients that are receiving short days' supply and patients that are receiving multiple gabapentin prescriptions each refill day. One patient was filling 3 different gabapentin prescriptions of different strengths at each refill date.

T5. Prescribers of patients with >400 days' supplied from Oct 1, 2018 - Sep 30, 2019

T6. Diagnosis codes submitted for potential inappropriate gabapentin use/prescribing/patients at increased risk for adverse outcomes for ALL patients; FFS is shown below.

Gabapentin fills (FFS) from Oct 1, 2018 - Sep 30, 2019	NUMBER OF PATIENTS WITH THESE DX								
	A	N	R	B	C	D	E	G	
	Any dx	EPILEPSY	POSTHER-PETIC NEURALGIA	RESTLESS LEG SYNDROME	ALCOHOL MISUSE	DRUG DEPENDENCE	DRUG ABUSE	POISONING	ACCIDENTAL POISONING
>1 Prescriber (GABA/Opioid) within 30 days	836	243	7	105	258	540	395	104	94
>1 Pharmacy (within 30 days	706	162	2	60	237	565	461	99	94
Patients with >3600mg/day*	26	12	1	2	6	21	17	6	4
Patients with >400 days' supply (year)♦	71	21	0	7	16	51	40	11	6
PATIENTS WITH Concurrent opioid (within 30 days)	1119	317	8	141	329	706	503	133	128
PATIENTS WITH Concurrent PREGABALIN (within 30 days)	156	36	0	15	43	125	94	23	20
PATIENTS WITH Concurrent benzodiazepine (within 30 days	1007	337	3	78	323	660	493	143	141
Patient with concurrent opioid and benzo (within 30 day	387	157	2	39	99	242	164	49	57
Patient with concurrent muscle relaxant (within 30 days)	910	239	10	111	267	585	416	96	92
Patient with concurrent hypnotic within 30 days)	210	56	1	28	55	143	112	34	32
Patient with concurrent opioid+benzo+ muscle relaxant+ hypnotic (within 30 days)	25	11	0	3	7	16	12	3	3

*Used single prescription to calculate this: (Quantity/day supply) x strength of formulation; this would not capture dosing of patients that received multiple prescriptions overlapping/different strength formulations on separate prescription. ♦This would be an overestimate if patients received multiple prescriptions overlapping/different strength formulations on separate prescriptions.

Conclusions

Abuse liability of gabapentin in the general population (1.1%) appears low compared to abuse prevalence rates involving other drugs.[10,95] Current or past substance abusers (particularly opioids), patients with psychiatric comorbidities, patients that are suicidal, patients that are vulnerable to the increased 'pro-drug' information on the web like children/adolescents, and inmates, may be at increased risk for abusing gabapentin. Prescribed gabapentin appear to be a major source of the abused/misused gabapentin. Some fatal overdoses have been reported where gabapentin was assumed to be the main cause of death. Concurrent use with opioids and other CNS depressants increases the risk for adverse outcomes. Doses needed for abuse-related effects include therapeutic doses, and supratherapeutic doses.[9,10,14,38,49,82]

Gabapentin is an important treatment option for many patients. This includes use in combination with opioids because it offers augmentation of opioid therapy although risk of adverse events increases and the risk/benefit ratio must be considered in any individual patient. It is important to ensure access where use may be warranted especially to help reduce the use of opioids. However, the risks of abuse/misuse and toxicity should be considered especially in populations at risk. Evidence on gabapentin's risk of misuse and abuse continue to emerge, requiring review of its use to identify any potential signs and risk factors for abuse.

Review of the Utah Medicaid Utilization data indicated that patients receiving gabapentin include patients that may be at increased risk for abusing gabapentin. Also, patients are receiving concurrent CNS drugs which may increase the risk of central nervous system and respiratory depression.

Appendix 1 – Drug information

Table 1. Summary of Gabapentin Dosing Recommendations

Source	Indication	Dosing
Neurontin (Gabapentin) Package Insert, FDA 2017[11]	Postherpetic Neuralgia	• Dose can be titrated up as needed to a dose of 1800 mg/day; efficacy was demonstrated with doses from 1800 mg/day to 3600 mg/day with comparable effects across the dose range
	Epilepsy with Partial Onset Seizures	• ≥ 12 years old: 900 to 1800 mg/day (in 3 divided doses) • See labeling for weight-based dosing for younger age groups
Horizant (gabapentin enacarbil) Package Insert, 2012	Restless Legs Syndrome	• 600 mg once daily taken at about 5 PM
	Postherpetic neuralgia in adults	• 600 mg in the morning for 3 days, then increase to 600 mg twice daily beginning on day 4
VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders, Department of Veterans Affairs and Department of Defense (2015)[96]	Alcohol Use Disorder	• Increase by 300mg daily as tolerated to target of 1800mg daily (in 3 divided doses)
Treatment of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report (Gibson et al., 2016)[65]	Chronic Refractory Cough	• 300 mg/day to 900 mg twice a day
Diabetic Neuropathy: A Position Statement by the American Diabetes Association (Pop-Busui et al., 2017)[71] Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation (2011)[70]	Diabetic Neuropathy	• IR formulation: 900 to 3600 mg/day in two or three divided doses

Source	Indication	Dosing
Pharmacotherapy for neuropathic pain in adults: systematic review, meta-analysis and updated NeuPSIG recommendations (Finnerup et al., 2015)[66] • Populations studied were those with postherpetic neuralgia, diabetic and non-diabetic painful polyneuropathy, postamputation pain, post-traumatic/postsurgical neuropathic pain including plexus avulsion and complex regional pain syndrome type II, central post-stroke pain, spinal cord injury pain, multiple sclerosis-associated pain and neuropathic pain associated with nociceptive components (eg, cancer neuropathic pain and radiculopathy) • Excluded conditions such as complex regional pain syndrome type I, low back pain without radicular pain, fibromyalgia, and atypical facial pain	Neuropathic Pain	• IR formulation: 1200 to 3600 mg/day in two or three divided doses • ER formulation: 300 to 600 mg/day in two divided doses
Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council (Chou et al., 2016)[72]	Postoperative Pain	• IR formulation: 300-1200mg as a single dose, given 1-2 prior to surgery or immediately after surgery; higher doses might be more effective but can increase risk of sedation
Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation (Garcia-Borreguero et al., 2016)[80]	Restless Leg Syndrome	• IR formulation: 900 -2400 mg/day • ER formulation: 600-1200 mg/day

Appendix 2 – Search strategy

Searches performed on 11/04/2019.

Pubmed

Search	Query	Items found	Notes
#7	Search #6 NOT ("Animals"[Mesh] NOT "Humans"[Mesh])	**1**	**Utah studies**
#6	Search #1 AND #5	1	
#5	Search Utah	63671	
#1	Search gabapentin AND (abuse OR misuse OR non-medical OR nonmedical OR illicit OR addict OR addiction OR diversion OR dependence OR drug-seeker OR drug-seeking OR trafficking OR inappropriate OR overprescribing OR overprescribed OR overprescribers OR overtreating OR overdiagnosis OR high)	1306	
#4	Search #2 OR #3	**141**	**Systematic Reviews**
#3	Search #1 and systematic[filter]	90	
#2	Search #1 AND ((((((((((("Meta-Analysis as Topic"[Mesh]) OR meta analy*[tw]) OR metaanaly*[tw]) OR Meta-Analysis[pt]) OR (((systematic AND (review* OR overview*)) AND tw))) OR "Review Literature as Topic"[Mesh])) OR (((((((cochrane[tiab]) OR embase[tiab]) OR ((psychlit OR psyclit[tiab])))) OR ((psychinfo OR psycinfo[tiab])))) OR ((cinahl OR cinhal[tiab])))) OR science citation index[tiab]) OR bids[tiab]) OR cancerlit[tiab])) OR (((((reference list*[tiab]) OR bibliograph*[tiab]) OR hand-search*[tiab]) OR relevant journals[tiab]) OR manual search*[tiab])) OR ((((selection criteria[tiab]) OR data extraction[tiab])) AND "Review"[pt]))) NOT ((((("Comment"[pt]) OR "Letter"[pt]) OR "Editorial"[pt]) OR (("Animals"[Mesh]) NOT (("Animals"[Mesh] AND "Humans"[Mesh]))))	125	

Query translation (#1; 1306 results)

("gabapentin"[MeSH Terms] OR "gabapentin"[All Fields]) AND (("substance-related disorders"[MeSH Terms] OR ("substance-related"[All Fields] AND "disorders"[All Fields]) OR "substance-related disorders"[All Fields] OR "abuse"[All Fields]) OR misuse[All Fields] OR non-medical[All Fields] OR nonmedical[All Fields] OR illicit[All Fields] OR addict[All Fields] OR ("behavior, addictive"[MeSH Terms] OR ("behavior"[All Fields] AND "addictive"[All Fields]) OR "addictive behavior"[All Fields] OR "addiction"[All Fields]) OR diversion[All Fields] OR ("dependency (psychology)"[MeSH Terms] OR ("dependency"[All Fields] AND "(psychology)"[All Fields]) OR "dependency (psychology)"[All Fields] OR "dependence"[All Fields]) OR drug-seeker[All Fields] OR ("drug-seeking behavior"[MeSH Terms] OR ("drug-seeking"[All Fields] AND "behavior"[All Fields]) OR "drug-seeking behavior"[All Fields] OR ("drug"[All Fields] AND "seeking"[All Fields]) OR "drug seeking"[All Fields]) OR trafficking[All Fields] OR inappropriate[All Fields] OR overprescribing[All Fields] OR overprescribed[All Fields] OR overprescribers[All Fields] OR overtreating[All Fields] OR ("medical overuse"[MeSH Terms] OR ("medical"[All Fields] AND "overuse"[All Fields]) OR "medical overuse"[All Fields] OR "overdiagnosis"[All Fields]) OR high[All Fields])

Translations:

gabapentin	"gabapentin"[MeSH Terms] OR "gabapentin"[All Fields]
abuse	"substance-related disorders"[MeSH Terms] OR ("substance-related"[All Fields] AND "disorders"[All Fields]) OR "substance-related disorders"[All Fields] OR "abuse"[All Fields]
addiction	"behavior, addictive"[MeSH Terms] OR ("behavior"[All Fields] AND "addictive"[All Fields]) OR "addictive behavior"[All Fields] OR "addiction"[All Fields]
dependence	"dependency (psychology)"[MeSH Terms] OR ("dependency"[All Fields] AND "(psychology)"[All Fields]) OR "dependency (psychology)"[All Fields] OR "dependence"[All Fields]

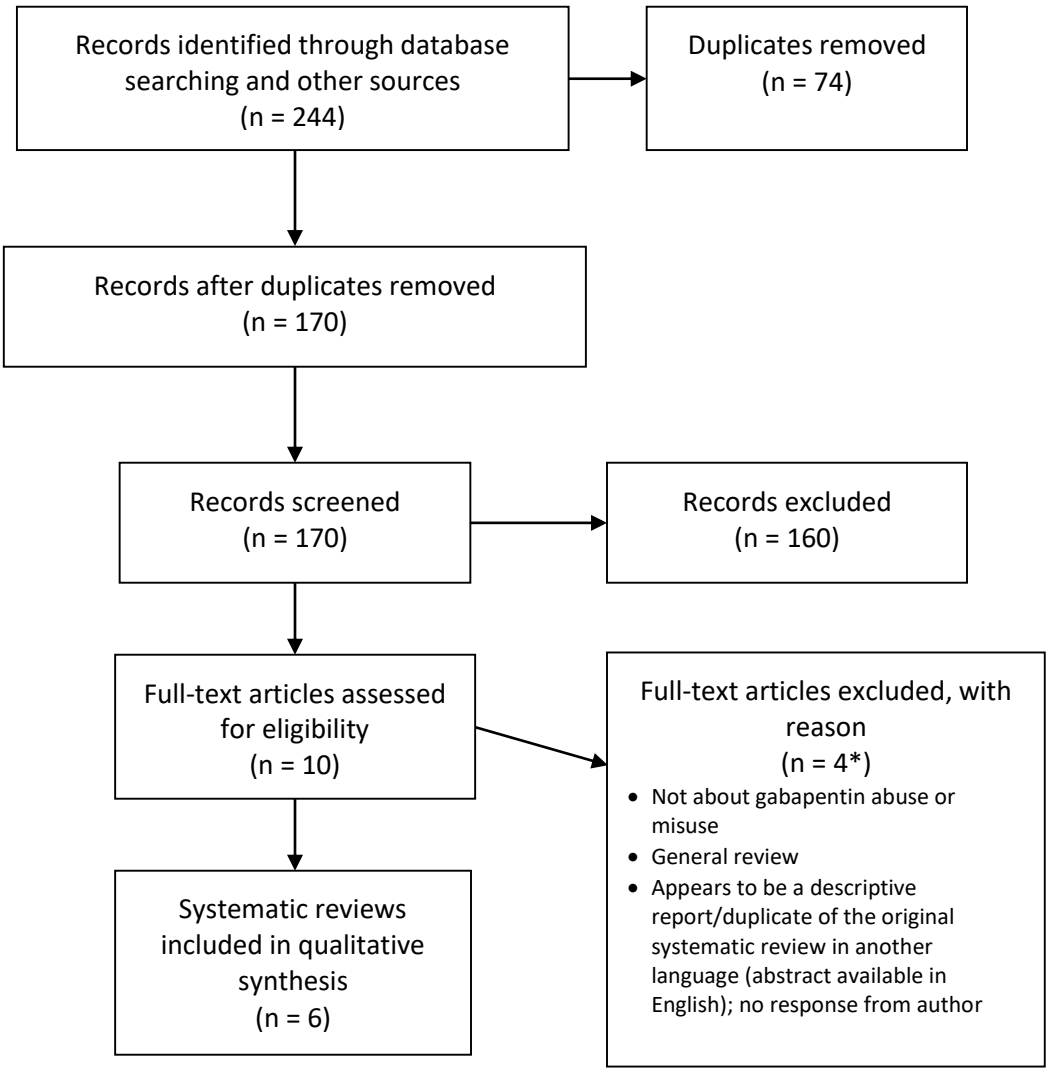
drug-seeking	"drug-seeking behavior"[MeSH Terms] OR ("drug-seeking"[All Fields] AND "behavior"[All Fields]) OR "drug-seeking behavior"[All Fields] OR ("drug"[All Fields] AND "seeking"[All Fields]) OR "drug seeking"[All Fields]
overdiagnosis	"medical overuse"[MeSH Terms] OR ("medical"[All Fields] AND "overuse"[All Fields]) OR "medical overuse"[All Fields] OR "overdiagnosis"[All Fields]

Epistemonikos

(title:(gabapentin) OR abstract:(gabapentin)) AND (title:(abus* OR misus* OR non-medical OR nonmedical OR illicit OR addict* OR diversion OR depend* OR drug-seek* OR trafficking OR inappropriate OR overprescrib* OR overtreat* OR overdiagnos* OR high) OR abstract:(abus* OR misus* OR non-medical OR nonmedical OR illicit OR addict* OR diversion OR depend* OR drug-seek* OR trafficking OR inappropriate OR overprescrib* OR overtreat* OR overdiagnos* OR high))
Limited to systematic reviews (105 results)

Figure 1 – PRISMA flowchart

Figure 1. Flow diagram for systematic reviews included



***List of excluded studies**

1. Vickers Smith R, Boland EM, Young AM, et al. A qualitative analysis of gabapentin misuse and diversion among people who use drugs in Appalachian Kentucky. *Psychology of Addictive Behaviors.* 2018;32(1):115-121.
2. Reinert JP, Dunn RL. Management of overdoses of loperamide, gabapentin, and modafinil: a literature review. *Expert Review of Clinical Pharmacology.* 2019;12(9):901-908.
3. Bonnet U, Scherbaum N. [On the risk of dependence on gabapentinoids]. *Fortschritte der Neurologie-Psychiatrie.* 2018;86(2):82-105.
4. Rudisill TM. Drug use and the risk of motor vehicle collision in adults 65 years of age and older. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2016;76(12-B(E)).

Appendix 3 – Systematic review evidence

Table 1. The Problem: Gabapentin abuse data from systematic reviews

Reference	Sources of abused/misused gabapentin	Drug effect sought by abusers/reasons for abuse or misuse	Toxic effects/Clinical presentation	Prevalence of gabapentin misuse or abuse	Overdoses/outcomes related to gabapentin abuse/misuse
DEA July 2019[8]	Annual total prescriptions for gabapentin increased over two-fold from 2,965,784 in 2011 to 6,722,145 in 2017 (IMS Health™). Commonly offered for sale from numerous websites.	To "get high"	FDA-labelled information Sedative and psychedelic effects (based on study that analyzed information from 32 websites)	15% of 503 adults reporting nonmedical use of pharmaceuticals 1.1% self-reported lifetime prevalence of gabapentin misuse (2013 online survey; 1500 respondents from UK; 16-59 years old) Rates of diversion steadily increased from 0.0 in 2002 to 0.027 cases per 100,000 population in 2015. 2016 Reports for gabapentin (6.5-6.75-fold increase from 2007) STARLiMS (web-based, commercial laboratory information management system) and STRIDE (System to Retrieve Information from Drug Evidence): 28 reports Federal databases for seized drugs analyzed by DEA forensic laboratories, and NFLIS (the National Forensic Laboratory Information System that collects drug analysis information from state, local, and other federal forensic laboratories): 2,219 reports.	AAPCC Involved in 168 fatalities in 2012-2016; gabapentin was primary cause in 23 individuals. Total gabapentin exposure calls: 72,283 (2012-2016); 5,889 (2012) and 20,064 (2016) Single substance exposure (gabapentin alone): increased from 2,141 (2012) to 7,024 (2016). DAWN ED visit rates (per 100,000 population) for gabapentin: increase from 2.7 (2004) to 4.9 (2011)

Reference	Sources of abused/misused gabapentin	Drug effect sought by abusers/reasons for abuse or misuse	Toxic effects/Clinical presentation	Prevalence of gabapentin misuse or abuse	Overdoses/outcomes related to gabapentin abuse/misuse
				RADARS system (Researched Abuse, Diversion and Addiction Related Surveillance System; prescription drug abuse/misuse and diversion monitoring system that collects geographically-specific data): 407 cases of gabapentin diversion were reported in 41 states between 2002 and 2015.	
Quintero 2017[38]	52% physicians, 36% drug dealers (US$1/pill)(Appalachian Kentucky)[94] Increase in number of patients asking for gabapentin (Scotland)[90]	Motivation for getting "high" To alleviate opioid withdrawal symptoms To potentiate methadone high	Route of administration impact side effects. Teratogenicity, hypoventilation, respiratory failure, deficits in visual field, myopathy, self-harm behavior, suicidal behavior, mitochondrial toxicity, somnolence, dizziness and asthenia.	1.1-19% 1.1% lifetime misuse (online UK survey; 1500 participants)[95] 4.8% misuse/abuse or dependence (EudraVigilance database; 2004-2015)[41] 15% misuse of 503 participants last 6 months (for getting high); used 25 of 30 previous days (Appalachian study in Kentucky)[94] 16% lifetime misuse (250 former inmates); 26% of patients with opioid disorder and 4% of patients without opioid use disorder.[97] 19% (25/129) use without prescription (Scotland survey)[98]	43 cases of gabapentin (postmortem toxicology analysis; 2010,2011 Finnish study); 18.6% of gabapentin findings associated with drug abuse; Gabapentin poisoning accounted for 4.7% of all gabapentin-related deaths. For those with drug abuse problems, 12.5% showed gabapentin poisoning. In the gabapentin abuser group, 87.5% of cases showed concomitant opioid use.[40] 86 gabapentin fatalities (EudraVigilance database; 2004-2015)[41]
Schifano 2018[26]	Increasing prescriptions and growing black market[10,27]	Psychoactive effects include a sense of well-being/relaxation, euphoria, and hallucinations.[100]		Increasingly being reported to be abused in the EU[10,27]; no specific levels	Increase in overdoses involving gabapentinoids (Emergency Department presentations involving intentional drug overdoses recorded by the National Self-Harm

Reference	Sources of abused/misused gabapentin	Drug effect sought by abusers/reasons for abuse or misuse	Toxic effects/Clinical presentation	Prevalence of gabapentin misuse or abuse	Overdoses/outcomes related to gabapentin abuse/misuse
	(Shutting 'rogue' pharmacies typically prompts sellers to move to servers in overseas countries, leading to a growing black market)[99]	("Within both online drug forum communities and social networks, there are some educated/informed users (the 'psychonauts')[29] who typically 'test' a range of psychotropics, including prescribed drugs, to achieve specific mindsets and eventually, share this information with peers.")[26,101]			Registry (Ireland; 2007–2015) Gabapentinoid fatalities are typically observed in combination with other psychoactive drugs (especially opioids and other sedatives)[91,102]
Evoy 2017	Prescription and non-prescription (street value $1-7 or may be traded for other drugs)[88,90,94,98] Most often obtained from healthcare providers (63.1%), family or acquaintances (57.8%), internet purchase (47.3%), and abroad (7.8%)[95] 40% of opioid dependent patients prescribed gabapentin admitted to misusing it (vs.13% without a prescription).[103] 22% of 29 patients in a Scottish methadone clinic used non-prescribed	To achieve euphoric highs (those abusing opioids that have developed tolerance may desire effects of new drugs) To become intoxicated or potentiate the effect of methadone, or buprenorphine/naloxone, and to avoid detection during routine urine drug screening (UDS monitoring)[88,91,97,98] Less common: to self-medicate uncontrolled pain, anxiety or withdrawal of other drugs/minimize cravings (e.g., cocaine, opioids or alcohol)	May differ based on tolerance and dose; supratherapeutic doses: sedation, dissociation, relaxation, contentment, numbness, uninhibited behavior, improved sociability, empathy, audio and visual hallucinations (anecdotal descriptions of users)	1.6% gabapentinoid abuse in general population; UK; 16-59 years old (1.1% gabapentin and 0.5% pregabalin)[95] 3-68% abuse among opioid abusers (15-22% gabapentin and 3-68% pregabalin) 11,940 reports of gabapentinoid abuse (4301 gabapentin and 7639 pregabalin) 2004-2015 (>75% reported since 2012) (international adverse event database).[41] 18.6% of gabapentin cases of Finnish autopsy cases involving gabapentinoids deemed drug abuse.[40]	High doses are generally not lethal, but gabapentinoids are increasingly identified in post-mortem toxicology analyses. 116 cases of gabapentin overdose; 23 for pregabalin; no deaths; mild-moderate severity outcomes; estimated median gabapentin dose 6000 mg (96000 mg max) (2002-2011 American poison center database)[104] 86/410 (21%) fatalities in patients abusing gabapentin (83 cases involved co-ingestants) (2004-mid-2015 International AE reporting system, Eudra-Vigilance); third of cases in 2014).[41] 36/48 post-mortem exams (Scotland) that included gabapentin also included methadone and/or morphine.[90]

Reference	Sources of abused/misused gabapentin	Drug effect sought by abusers/reasons for abuse or misuse	Toxic effects/Clinical presentation	Prevalence of gabapentin misuse or abuse	Overdoses/outcomes related to gabapentin abuse/misuse
	gabapentinoids (19% gabapentin).[98]				Gabapentinoids found in 2.61% of 13,766 autopsies (Finland); 43 (0.31%) gabapentin identified cases.[40]
Marsden 2019[82]	This mixed-method public health review focuses on the dependence or withdrawal of prescribed medicines (including gabapentin) Prescriptions for gabapentinoids increased from 2.7 million in 2008 to 14.4 million in 2018.	Report in introduction that early reports for gabapentinoids included euphoria, sedation and dissociation and thought to have a low risk of dependence and withdrawal.[9,10] but recent evidence shows the risks when taken with opioids (dangerous respiratory depression).[105]	NR	Long-term prescribing is common	Little evidence was found for withdrawal for gabapentinoids; no specific information for gabapentin.
Smith 2016[9]	Major source is health services/physicians (52-63% in UK and US)[94,95](prescriptions, own medication), family, friend, internet/online pharmacies, abroad, drug dealers (street market 1 GBP per 300 mg, 1-7 US$ per pill depending on strength) [39,49,94,95,98,106-109]	Primarily for recreational purposes, self-medication or intentional harm (suicide) To potentiate the effects of methadone.[98] Used as a cutting agent for heroin.[90] Substitute for cocaine.[88,110] Several subjective experiences reminiscent of opioids, benzodiazepines and psychedelics were reported (to be interpreted with caution): Feeling 'high' (cocaine-like 'high') or 'stoned' 'amphetamine rush', 'fully sedated opiate buzz', 'disassociation like DXM', 'talkative', 'comparable to cannabis',	Various including CNS symptoms, GI symptoms, cardiac symptoms, neuromuscular symptoms, seizures, nystagmus, coma, respiratory depression	1.1% in general population (UK);[95] 40–65% among individuals with prescriptions[94,95,103,106] and between 15 and 22% within populations of people who abuse opioids.[94,98,103]	Scotland (2010): Approximately 1% of all drug-related deaths were attributed directly to gabapentin.[98] 0.6% of 23, 479 impaired driving cases in the United States involved gabapentin (Washington state 2003-2007).[111] Gabapentin in 0.3% of 13 766 medico-legal postmortem case investigations (Finland).[40]

Reference	Sources of abused/misused gabapentin	Drug effect sought by abusers/reasons for abuse or misuse	Toxic effects/Clinical presentation	Prevalence of gabapentin misuse or abuse	Overdoses/outcomes related to gabapentin abuse/misuse
		'buzz slightly reminiscent of MDMA', euphoria, improved sociability, a marijuana-like 'high', relaxation, sense of calm, 'zombie-like' effects, increased energy and focus, and improved sleep.			
Bonnet and Scherbaum 2017[14]	Prescriptions (good portion off-label use), internet, black markets	To get high, to potentiate an opioid high or to dampen withdrawal symptoms or anxiety. Authors state robust evidence that opioid users (including multiple drug users) selected gabapentinoids mainly to boost a euphoric high and reduce withdrawal symptoms while producing only few adverse effects.[49,94,97,98,103]	Refer to overdose cases	Rough estimation for general population Life-prevalence of dependence: 0.25% (elderly German hospital population)[112] Life-prevalence of misuse: 0.5–1.1%, (younger British internet-population).[95] 15-22% for opioid dependent/using (self-administering) patients and those in opioid substitution programs (up-to-6-month rates)[94,97,98]	Recommended maximum therapeutic blood level is 30 mg/L.[113] <u>Nonfatal overdoses</u> 9 case presentations (table 3) and one case series mostly in combination with other drugs.[106] Highest described blood levels were nearly 4-fold the recommended maximum therapeutic blood level (2 cases: coma, respiratory depression or cardiopulmonary resuscitation but also related to overdosing with concurrent medications).[114,115] Two case reports for gabapentin alone with lower blood levels: 62mg/L[39] and 72.8mg/L[116] with sedation and nausea but stable vital signs. One case[117] of a 30-year-old woman with epilepsy and renal insufficiency with blood concentrations of nearly 3-times the maximum level) after a dose increase to 1800 mg daily together with valproate: developed mild resting tremor and cognitive deficits

Reference	Sources of abused/misused gabapentin	Drug effect sought by abusers/reasons for abuse or misuse	Toxic effects/Clinical presentation	Prevalence of gabapentin misuse or abuse	Overdoses/outcomes related to gabapentin abuse/misuse
					Overdoses together with other substances were more toxic; parenteral applications of gabapentin is described by others.[49] <u>Fatal overdoses:</u> 6 postmortem case reports with gabapentin assumed to be the main cause of death.[41,108,118,119] 2 of these cases involved excessive and pure gabapentin (alone) self-poisoning.[108,119] American Association of Poison Control Centers (2012–2015)[120-123]: total fatality rates have been falling, but gabapentinoid-related fatalities had increased from 1.5% (n=38; 31 is gabapentin) to 4.3% (n=59; 51 is gabapentin)

Table 2. Targets for interventions: Gabapentin abuse data from systematic reviews

Reference	Populations at increased risk for misuse or abuse	Doses needed for abuse-related effects	Factors increasing the abuse effect/risk for overdose or death
DEA July 2019	Based on 2 studies reported in prevalence section, it appears possibly higher in "nonmedical users of pharmaceuticals"	NR	NR, but they state: Gabapentin is not currently a Controlled Substance. Increase in number of prescriptions (>double from 2011 to 2017) Commonly offered for sale online

Reference	Populations at increased risk for misuse or abuse	Doses needed for abuse-related effects	Factors increasing the abuse effect/risk for overdose or death
Quintero 2017[38]	5.2% of patients attending misuse services for at least 4 years had prescription for gabapentin and these subjects were at least 3 times more likely to accept misuse of analgesics (P=0.0006; Scotland study)[90] Misuse/abuse or dependence mainly women (EudraVigilance database; 2004-2015)[41] Patients with opioid disorder (26% vs. 4% without opioid use disorder).[97]	Average dose of patients (described in population column; Scotland study) was 1343 mg.[90]	Majority of fatalities consisted of a combination of gabapentin and opioids (EudraVigilance database; 2004-2015)[41]
Schifano 2018[26]	Patients that are suicidal (Intentional drug overdoses recorded by the National Self-Harm Registry (Ireland; 2007–2015), showed that gabapentinoids have been increasingly identified over time)[124] Patients that are vulnerable to the increased 'pro-drug' information on the web (with increased access to the web) like children/adolescents and psychiatric patients[101] Inmates or people with a misuse or abuse history (systematic review authors' conclusion)[26]	1000-4800 mg alone or in combination with other drugs based on reports from "web enthusiasts"[26,125] Potential strategy: Identify a repeat supply issue (authors of systematic review)[26]	High dosages and polydrug abuse (especially opioids and other sedatives whose effects are potentiated by gabapentinoids)[91,102,124]
Evoy 2017[10]	Current or past substance abusers (particularly opioids, but also past cocaine use,[39,88,110,126] concurrent use with cannabis,[98] benzodiazepine,[94,98] and as a cutting agent for heroin[90]) and psychiatric comorbidities (risk factor for most drugs of abuse, but increase prevalence in gabapentin abuse may be due to off-label use for psychiatric conditions).[90,97,98,103] Former inmates with both psychiatric and SUD diagnoses (41/250=16% of those surveyed misused gabapentin); 26% (37/145) of those with opioid use disorder vs.4% (4/105) without.[97]	Typically involves supratherapeutic doses (often in clear excess of the max recommended dose of 3600 mg/day) 600 and 1200 mg produced similar drug-liking to oral tetrahydrocannabinol (THC; active of cannabis) and increased THC drug-liking when administered concurrently (8 cannabis users)[127] Median dose of 9 case reports/series (14 patients) of gabapentin abuse was 3600 mg (range of 1500-12,000 mg)[88,89,91,109,110,126,128-130]	Deaths more common when coingested with other CNS depressants. Most gabapentinoid-related fatalities involve opioids.[41] Opioids found in 87.5% of gabapentin abuse cases of Finnish autopsy cases involving gabapentinoids.[40] (there were 43 gabapentin identified cases and 18.6% were attributed to drug abuse) Mostly taken orally, but other routes have been reported including injecting, smoking, or inhaling crushed tablets, rectal plugging, or parachuting (emptying crushed tablets or capsule contents into a pouch (e.g., toilet paper) and swallowing, in order to absorb larger quantities at one time while avoiding

Reference	Populations at increased risk for misuse or abuse	Doses needed for abuse-related effects	Factors increasing the abuse effect/risk for overdose or death
	Widespread diversion and highly sought after drug in prisons (US and Scotland)[98,126] Scotland study shows patients in substance misuse services prescribed gabapentin were >3 times more likely to admit to non-medical use of analgesics.[90] Typical gabapentin abusers are young (30 vs 58 years old in a Finnish study).[40] Conflicting data regarding gender abuse differences, but cite pregabalin and gabapentin studies (the authors mention the Eudravigilance data indicating more females, but substantially more women were included in the total number of adverse drug reactions;[41] also, a study in opioid abusers in which 77.8% of patients that tested positive for gabapentin were female[94])	When abused doses are typically not taken as 3-4 divided doses/day, but as a single supratherapeutic dose. Due to quick development of tachyphylaxis, repeat users may continue to increase the dose. Frequency of gabapentinoid abuse General population (survey): 13.1% >once weekly; 50% once weekly–once monthly; 36.8% less frequently.[95] Opioid abusers use an average of 25 of the past 30 days (survey).[94]	the taste of the drug.[126,131] (some information may apply to pregabalin) Concurrent abuse of other drugs
Marsden 2019[82]	Refer to factors (mental health diagnosis and OUD)	NR	They mention evidence of dangerous respiratory depression when gabapentinoids are taken with opioids (introduction)[37] They reported on studies identified for factors that contribute to the risk of harms associated with dependence and the short term discontinuation or longer term withdrawal symptoms from opioids for chronic pain (excluding end of life /palliative care/cancer pain), benzodiazepines, Z-drugs, gabapentin and pregabalin (excluding epilepsy treatment), and antidepressants. No specific findings were reported for gabapentin.
Smith 2016[9]	Authors of review: Individuals with histories of drug abuse. Based on information found in review (interpretation): Individuals with a history of alcohol abuse or dependence do not appear to be at increased risk.[103]	A range of doses, including those within clinical recommendations (900-3600 mg) and supratherapeutic doses. For euphoria reminiscent of, but not as strong as opioids (gabapentin used alone or	Most commonly found substances with gabapentin include alcohol[49] and/or opioids (2010-2011 Finnish postmortem toxicological samples),[40] morphine and methadone (75% of gabapentin postmortem toxicology reports cases in Scotland),[90] and polysubstances in driving impairment cases

Reference	Populations at increased risk for misuse or abuse	Doses needed for abuse-related effects	Factors increasing the abuse effect/risk for overdose or death
	Possibly inmates: Only 19/96 prescriptions amongst inmates were in the possession of the person that received the prescription.[126]	in combination with other drugs e.g. buprenorphine/naloxone, methadone, baclofen, quetiapine, alcohol) actual abused dosage ranges were provided by 3 papers ranging from 1500 to 12000 mg.[88,91,130] For sedation/relaxation/calmness (alone or in combination with other drugs e.g. quetiapine, alcohol, cannabis, buprenorphine/naloxone) a range of 600-4800 mg was reported. Based on some studies, those with prescriptions use more than prescribed (potentially due to tolerance and addiction),[40,89,103,129] and those without prescription often took doses within clinical recommendation limits, but doses were not spread out during the day and frequency of dosing was unclear.[88]	(benzodiazepines (44%), opioids (43%), antidepressants (43%), other central nervous system (CNS) depressants (e.g. trazodone, zolpidem; 36%), anti-epileptics (25%), cannabinoids (15%), stimulants (11%) and ethanol (6%)(Washington State in 2003-2007),[111] and cannabis, selective serotonin reuptake inhibitors (SSRIs), lysergic acid diethylamide (LSD), amphetamine and GHB (gammahydroxybutyric acid) (review).[49] Those misusing gabapentin may also be misusing buprenorphine.[94] Substance abuse populations: greater likelihood for those misusing gabapentin to also be misusing prescription opioids and benzodiazepines.[90]
Bonnet and Scherbaum 2017[14]	Opioid using (self-administering) patients and those in opioid substitution programs		Overdoses together with other substances Gabapentin not regulated by law. "In comparison with propofol and benzodiazepines, gabapentinoids are certainly the safest GABAmimetics with a higher therapeutic index and wider dose margin between pleasure (euphoria/relaxation) and coma or death by overdosing."[10,14,37,38]

Table 3. Implications of lack of or failed interventions (to prevent abuse and adverse consequences): Gabapentin abuse data from systematic reviews

Reference	Management of intoxication	Cost associated with overdose e.g., hospitalizations
DEA July 2019[8]	NR	NR
Quintero 2017[38]	NR	NR
Schifano 2018[26]	NR	NR
Evoy 2017[10]	Appears relatively safe even following acute overdose; common symptoms include hypotension, tachycardia, CNS effects (more severe than with therapeutic doses); Rare reports of fatalities or intensive care unit admissions (ICU); outcomes are generally mild-moderate even with high doses (as high as 96,000 mg); symptoms typically resolved within 10 hours in case series; reports of patients surviving 91000 mg (25 times max dose) even with coingestion of other substances; severe cases may be more common with renal impairment.[39,40,104,106,108,114-117,119,132-134]	No patients requiring hospitalization in a US Poison center study of 20 gabapentin exposure.[106]
Marsden 2019[82]	They reviewed several aspects of dependence or withdrawal, including management, prevention and treatment approaches, patient experiences, and support services (including opioids, benzodiazepines, antidepressants, Z-drugs, and gabapentinoids), but did not report any specific information for gabapentin about these aspects in the manuscript.	NR
Smith 2016[9]	NR	NR
Bonnet and Scherbaum 2017[14]	NR	NR

Appendix 4 – Utah Poison Control Center: Gabapentin exposures

Utah Poison Control Center

Gabapentin exposures

January 1, 2014 – September 30, 2019

The Utah Poison Control Center (UPCC) was consulted on the management of 2,011 cases involving gabapentin between January 1, 2014 and September 30, 2019.

Year	Gabapentin	Total UPCC Human Exposures	Gabapentin exposures (% of total)	Intentional Exposures	total intentional exposures	% intentional exposures
2014	260	41,012	0.6	153	4817	3.2
2015	306	41,210	0.7	179	5048	3.5
2016	278	41,509	0.7	177	5438	3.3
2017	417	39,474	1.1	260	5809	4.5
2018	411	39,730	1.0	264	6113	4.3
2019*	339	31,038	1.1	218	4879	4.5
Total	**2,011**	**233,973**	**0.9**	**1,251**	**32,104**	**3.9**

I. Gabapentin

A. Reason for exposure

The reason for exposure is documented by the specialist in poison information and is based on the history, circumstances and other evidence during the course of the poison center involvement with the case - which is typically until the situation has resolved (home cases) or the patient is medically cleared. It is sometimes difficult to discern true intent – specifically discerning between intentional misuse, abuse or intentional suicide. The poison center utilizes psychiatry consultation notes whenever possible to try to accurately define the reason when the situation is unclear.

- Unintentional (664; 33%)
  - Unintentional general (exploratory behavior/dementia): 211(10.5%)
  - Therapeutic error: 446 (22.2%)
- Intentional (1,251; 62.2%)
  - Suspected suicide: 1,013 (50.4%)

    - Misuse: 112 (5.6%)
    - Abuse: 71 (3.5%)
  - Other (22; 1.1%)
  - Adverse reaction (59; 2.9%)
  - Unknown (15; 0.8%)

Reason by Age

- All but one case involving children <= 5 years was coded as unintentional.
  - 95% unintentional general (oral exploration)
  - 4.5% therapeutic error
  - 1 case was coded as Other – specifically concern for withdrawal (likely a newborn)
- 6-12 years of age
  - 66.7% unintentional with the majority coded as therapeutic error
  - 6 (28.6%) were coded as intentional – with suicide attempt the reason in 2/3
- 13-19 years of age
  - 136 (84%) of cases in this age group were for intentional reason – with the majority suicide attempt.
- Adults
  - The majority (68%) were coded as intentional with suicide the most common intentional code. Abuse was coded in only 3.5% of adult cases.

B. Age and Gender

- 202 (9.95%) <= 5 years of age
- 1623 (80.71%) >= 20 years of age
- 1,193 (59.32%) female
- ~ 60% of all exposures reported to UPCC involve children <= 5 years of age.

C. Caller, Exposure and Management Site

- 1,807 (89.8%) of exposures occurred at a residence
- 1,105 (54.9%) consults originated from a health care facility
- 525 (26.1%) of exposures were managed onsite
- 1,374 (68.3%) of exposures were managed in a healthcare facility
  - 479 (22.8%) treated and released from emergency department
  - 314 (15.6%) admitted for critical care unit
  - 211 (10.5%) admitted to noncritical care unit
  - 312 (15.5%) admitted to psychiatric facility

D. Medical Outcome

- 447 (22.2%): no effect
- 799 (39.7%): minor effect
- 413 (20.5%): moderate effect

- 91 (4.5%): major effect
- 3 (0.2%): death
- 177 (8.8%): not or unable to follow
- 81 (4%): effects unrelated to exposure

E. Additional Substances

The Utah Poison Control Center captures all potential substances involved in a poisoning exposure. More than one substance is involved in the majority of self-harm attempts. The following substances were also involved in cases involving gabapentin. The numbers reflect the number of times the substance was documented on a record and not the number of patients. The prescription status of the medications is unknown.

1. Non-pharmaceutical substances – 224 substance occurrences
   - Ethanol 208 (92.3%) of occurrences

2. Pharmaceutical substances – 5,602 substance occurrences
   - Analgesics – 475 occurrences
     - Opioids (144); with APAP (86)
   - Anticonvulsants (other than gabapentin) = 233 occurrences
   - Antidepressants = 672 occurrences
   - Antihistamines = 186 occurrences
   - Cardiovascular drugs = 384 occurrences
   - Muscle relaxants = 153 occurrences
   - Hormones (includes diabetic drugs) = 157 occurrences
   - Sedative hypnotic/antipsychotic agents = 721 occurrences
     - Benzodiazepines = 291 occurrences
   - Stimulants and street drugs = 114 occurrences
     - Amphetamine/methamphetamine = 57 occurrences
     - Heroin = 15 occurrences

Appendix 5 - Additional data

Table 1. All claims

ALL FILLS		2016		2017		2018		2019		Total	
	Product	Patients	Claims	Patients	Claims	Patients	Claims	Patients	Claims	Patients	Claims
Gabapentin	GABAPENTIN CAP 100MG	1606	4901	1662	4933	1811	5553	1878	5225	5384	20612
Gabapentin	GABAPENTIN CAP 300MG	5401	21521	5448	21667	5965	23659	6165	21775	15034	88622
Gabapentin	GABAPENTIN CAP 400MG	861	3782	839	3745	978	4305	1109	4136	2591	15968
Gabapentin	GABAPENTIN SOL 250/5ML	217	1103	226	1304	281	1580	273	1398	590	5385
Gabapentin	GABAPENTIN SOL 300/6ML	.	.	.	.	1	1	.	.	1	1
Gabapentin	GABAPENTIN TAB 600MG	2587	13497	2550	13400	2991	15412	3441	14541	6932	56850
Gabapentin	GABAPENTIN TAB 800MG	1477	8682	1548	9392	2032	11408	2415	11659	4082	41141
Gabapentin	NEURONTIN CAP 100MG	1	5	.	.	.	.	.	.	1	5
Gabapentin	NEURONTIN CAP 300MG	3	37	3	37	1	10	1	9	3	93
Gabapentin	NEURONTIN SOL 250/5ML	2	19	2	18	2	21	2	22	2	80
Gabapentin	NEURONTIN TAB 800MG	2	15	1	8	1	8	1	7	2	38
Gabapentin (Bulk)	GABAPENTIN POW	1	1	1	4	.	.	.	.	2	5
Gabapentin (Once-Daily)	GRALISE TAB 600MG	3	29	5	26	3	32	4	24	6	111
Gabapentin Enacarbil	HORIZANT TAB 600MG ER	2	5	1	10	3	17	1	9	5	41
Total	Total	9884	53597	9991	54544	11393	62006	12447	58805	24612	228952

(Only products with claims/utilization are shown)

Table 2. FFS claims

	2016		2017		2018		2019		Total	
Product	Patients	Claims	Patients	Claims	Patients	Claims	Patients	Claims	Patients	Claims
GABAPENTIN CAP 100MG	529	1451	556	1441	622	1715	833	2010	2123	6617
GABAPENTIN CAP 300MG	1928	6390	1935	6359	2554	8123	3203	9259	7218	30131
GABAPENTIN CAP 400MG	319	1101	304	1016	432	1458	604	1811	1307	5386
GABAPENTIN SOL 250/5ML	60	270	73	348	86	526	100	501	209	1645
GABAPENTIN TAB 600MG	982	4018	925	3890	1452	5854	2011	6928	3804	20690
GABAPENTIN TAB 800MG	530	2290	547	2202	1043	4308	1470	5765	2470	14565
NEURONTIN CAP 300MG	1	2	.	.	.	.	.	.	1	2
GABAPENTIN POW	1	1	.	.	.	.	.	.	1	1

	2016		2017		2018		2019		Total	
Product	Patients	Claims	Patients	Claims	Patients	Claims	Patients	Claims	Patients	Claims
GRALISE TAB 600MG	.	.	.	.	.	.	1	1	1	1
HORIZANT TAB 600MG ER	.	.	.	.	1	1	.	.	1	1
Total	3695	15523	3697	15256	5099	21985	6690	26275	12999	79039

Table 3. Pediatric claims

ALL PEDIATRIC CLAIMS

		2016		2017		2018		2019		ALL	
AGENT	**PRODUCT**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**
Gabapentin	GABAPENTIN CAP 100MG	589	163	680	200	858	241	605	175	**2,732**	**564**
Gabapentin	GABAPENTIN CAP 300MG	476	128	499	156	583	175	491	146	**2,049**	**453**
Gabapentin	GABAPENTIN CAP 400MG	143	27	160	33	170	36	83	24	**556**	**77**
Gabapentin	GABAPENTIN SOL 250/5ML	789	154	942	157	1194	209	1047	196	**3,972**	**402**
Gabapentin	GABAPENTIN TAB 600MG	224	29	180	36	156	37	102	26	**662**	**89**
Gabapentin	GABAPENTIN TAB 800MG	38	8	34	13	37	7	26	6	**135**	**22**
Gabapentin	NEURONTIN SOL 250/5ML	12	1	14	1	13	1	12	1	**51**	**1**
Total		2271	448	2509	513	3011	617	2366	505	**10,157**	**1,323**

FFS PEDIATRIC CLAIMS

		2016		2017		2018		2019		ALL	
AGENT	**PRODUCT**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**
Gabapentin	GABAPENTIN CAP 100MG	111	33	118	42	159	40	137	34	**525**	**107**
Gabapentin	GABAPENTIN CAP 300MG	56	17	52	24	89	31	106	39	**303**	**92**
Gabapentin	GABAPENTIN CAP 400MG	15	6	38	6	20	7	4	3	**77**	**15**
Gabapentin	GABAPENTIN SOL 250/5ML	165	37	253	50	403	66	362	65	**1,183**	**131**
Gabapentin	GABAPENTIN TAB 600MG	23	4	26	6	34	9	31	11	**114**	**22**

FFS PEDIATRIC CLAIMS

		2016		2017		2018		2019		ALL	
AGENT	**PRODUCT**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**
Gabapentin	GABAPENTIN TAB 800MG	8	3	2	1	4	2	5	1	**19**	**7**
Total		378	88	489	115	709	142	645	138	**2,221**	**323**

Table 4. Number of pediatric patients by age and diagnosis codes

DX	DESCRIPTION
A	EPILEPSY
N	POSTHERPETIC NEURALGIA
R	RESTLESS LEG SYNDROME
B	ALCOHOL MISUSE
C	DRUG DEPENDENCE
D	DRUG ABUSE
E	POISONING (any substance)
G	ACCIDENTAL POISONING (subset of poisoning)

Definitions/list of diagnosis codes included in each category available on request.

GABAPENTIN ALL PEDIATRIC PATIENTS																	
TOTAL PATIENTS 2016-2019																	
AGE*	**M**	**F**	**Total**	**DX A**	**PERCENT**	**DX R**	**PERCENT**	**DX B**	**PERCENT**	**DX C**	**PERCENT**	**DX D**	**PERCENT**	**DX E**	**PERCENT**	**DX G**	**PERCENT**
0	27	15	42	10	23.8%	.	.	.	.	5	11.9%	.	.	.	.	.	.
1	19	7	26	6	23.1%	.	.	.	.	1	3.8%	.	.	.	.	.	.
2	23	20	43	15	34.9%	1	2.3%	.	.	1	2.3%	.	.	.	.	.	.
3	16	15	31	14	45.2%	.	.	.	.	1	3.2%	.	.	.	.	.	.
4	19	13	32	9	28.1%	.	.	.	.	.	.	.	.	.	.	.	.
5	23	23	46	11	23.9%	1	2.2%	.	.	.	.	.	.	.	.	1	2.2%
6	15	14	29	6	20.7%	1	3.4%	.	.	.	.	.	.	.	.	.	.
7	21	13	34	6	17.6%	.	.	.	.	.	.	.	.	.	.	.	.
8	27	17	44	9	20.5%	.	.	.	.	.	.	.	.	1	2.3%	.	.
9	22	18	40	5	12.5%	.	.	.	.	.	.	.	.	.	.	.	.
10	24	24	48	9	18.8%	.	.	.	.	1	2.1%	1	2.1%	.	.	.	.
11	47	26	73	12	16.4%	.	.	.	.	.	.	1	1.4%	1	1.4%	1	1.4%
12	43	32	75	15	20.0%	.	.	.	.	1	1.3%	.	.	.	.	.	.

GABAPENTIN ALL PEDIATRIC PATIENTS																	
TOTAL PATIENTS 2016-2019																	
AGE*	**M**	**F**	**Total**	**DX A**	**PERCENT**	**DX R**	**PERCENT**	**DX B**	**PERCENT**	**DX C**	**PERCENT**	**DX D**	**PERCENT**	**DX E**	**PERCENT**	**DX G**	**PERCENT**
13	39	50	89	8	9.0%	1	1.1%	.	.	2	2.2%	6	6.7%	4	4.5%	1	1.1%
14	52	74	126	8	6.3%	.	.	.	.	4	3.2%	7	5.6%	2	1.6%	4	3.2%
15	57	90	147	12	8.2%	.	.	7	4.8%	5	3.4%	17	11.6%	12	8.2%	4	2.7%
16	70	118	188	9	4.8%	1	0.5%	10	5.3%	8	4.3%	18	9.6%	10	5.3%	2	1.1%
17	80	130	210	13	6.2%	3	1.4%	7	3.3%	16	7.6%	25	11.9%	11	5.2%	4	1.9%
TOTAL	624	699															
* Age at first claim.																	

GABAPENTIN FFS PEDIATRIC PATIENTS																	
TOTAL PATIENTS 2016-2019																	
AGE*	**M**	**F**	**Total**	**DX A**	**PERCENT**	**DX R**	**PERCENT**	**DX B**	**PERCENT**	**DX C**	**PERCENT**	**DX D**	**PERCENT**	**DX E**	**PERCENT**	**DX G**	**PERCENT**
0	12	4	16	7	43.8%	.	.	.	.	3	18.8%	.	.	.	.	.	.
1	6	3	9	4	44.4%	.	.	.	.	1	11.1%	.	.	.	.	.	.
2	9	11	20	13	65.0%	1	5.0%	.	.	1	5.0%	.	.	.	.	.	.
3	7	6	13	8	61.5%	.	.	.	.	1	7.7%	.	.	.	.	.	.
4	6	5	11	6	54.5%	.	.	.	.	.	.	.	.	.	.	.	.
5	7	8	15	10	66.7%	1	6.7%	.	.	.	.	.	.	.	.	.	.
6	3	6	9	3	33.3%	1	11.1%	.	.	.	.	.	.	.	.	.	.
7	6	9	15	6	40.0%	.	.	.	.	.	.	.	.	.	.	.	.
8	.	2	2	1	50.0%	.	.	.	.	.	.	.	.	.	.	.	.
9	7	4	11	5	45.5%	.	.	.	.	.	.	.	.	1	9.1%	.	.
10	6	5	11	4	36.4%	.	.	.	.	.	.	.	.	.	.	.	.
11	11	6	17	5	29.4%	.	.	.	.	1	5.9%	1	5.9%	1	5.9%	1	5.9%
12	7	8	15	9	60.0%	.	.	.	.	.	.	.	.	.	.	.	.
13	8	12	20	6	30.0%	1	5.0%	.	.	.	.	1	5.0%	1	5.0%	1	5.0%
14	8	16	24	3	12.5%	.	.	.	.	.	.	3	12.5%	1	4.2%	2	8.3%
15	15	21	36	5	13.9%	.	.	1	2.8%	2	5.6%	5	13.9%	4	11.1%	2	5.6%
16	9	29	38	4	10.5%	1	2.6%	3	7.9%	1	2.6%	5	13.2%	2	5.3%	1	2.6%
17	24	17	41	2	4.9%	1	2.4%	6	14.6%	9	22.0%	12	29.3%	4	9.8%	2	4.9%

GABAPENTIN FFS PEDIATRIC PATIENTS																	
TOTAL PATIENTS 2016-2019																	
AGE*	M	F	Total	DX A	PERCENT	DX R	PERCENT	DX B	PERCENT	DX C	PERCENT	DX D	PERCENT	DX E	PERCENT	DX G	PERCENT
TOTAL	151	172															
* Age at first claim.																	

Table 5. Diagnosis codes submitted (adult and pediatric patients)

A EPILEPSY/SEIZURES
N POSTHERPETIC NEURALGIA
R RESTLESS LEG SYNDROME
B ALCOHOL MISUSE
C DRUG DEPENDENCE
D DRUG ABUSE
E POISONING (any substance)
G ACCIDENTAL POISONING (subset of poisoning)
Definitions/list of diagnosis codes included in each category available on request.

Gabapentin - ALL CLAIMS 2016-2019																			
AGENT	PRODUCT	CLAIMS	PATIENTS	DX A		DX N		DX R*		DX B		DX C		DX D		DX E		DX G	
Gabapentin	GABAPENTIN CAP 100MG	**20,612**	**5,384**	444	8.2%	4	0.07%	137	2.54%	420	7.80%	790	14.67%	552	10.25%	222	4.12%	131	2.43%
Gabapentin	GABAPENTIN CAP 300MG	**88,622**	**15,034**	1,238	8.2%	15	0.10%	413	2.75%	1,526	10.15%	3,147	20.93%	2,216	14.74%	632	4.20%	483	3.21%
Gabapentin	GABAPENTIN CAP 400MG	**15,968**	**2,591**	312	12.0%	7	0.27%	96	3.71%	365	14.09%	839	32.38%	599	23.12%	210	8.11%	158	6.10%
Gabapentin	GABAPENTIN SOL 250/5ML	**5,385**	**590**	163	27.6%	.	.	6	1.02%	17	2.88%	28	4.75%	16	2.71%	7	1.19%	9	1.53%
Gabapentin	GABAPENTIN SOL 300/6ML	**1**	**1**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Gabapentin	GABAPENTIN TAB 600MG	**56,850**	**6,932**	738	10.6%	14	0.20%	236	3.40%	877	12.65%	2,153	31.06%	1,508	21.75%	441	6.36%	336	4.85%
Gabapentin	GABAPENTIN TAB 800MG	**41,141**	**4,082**	484	11.9%	8	0.20%	162	3.97%	556	13.62%	1,641	40.20%	1,224	29.99%	354	8.67%	275	6.74%
Gabapentin	NEURONTIN CAP 100MG	**5**	**1**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Gabapentin	NEURONTIN CAP 300MG	**93**	**3**	1	33.3%	.	.	.	.	.	.	1	33.33%	.	.	1	33.33%	.	.
Gabapentin	NEURONTIN SOL 250/5ML	**80**	**2**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Gabapentin	NEURONTIN TAB 800MG	**38**	**2**	1	50.0%	.	.	.	.	.	.	.	.	.	.	1	50.00%	.	.
Gabapentin (Bulk)	GABAPENTIN POW	**5**	**2**	.	.	.	.	.	.	.	.	1	50.00%	.	.	.	.	.	.
Gabapentin (Once-Daily)	GRALISE TAB 600MG	**111**	**6**	.	.	.	.	.	.	.	.	1	16.67%	.	.	1	16.67%	.	.
Gabapentin Enacarbil	HORIZANT TAB 600MG ER	**41**	**5**	.	.	.	.			.	.	.	.	.	.	.	.	.	.
	TOTALS	**228,952**	**24,612**	2,137	8.7%	26	0.11%	678	2.75%	2,378	9.66%	5,221	21.21%	3,739	15.19%	1,078	4.38%	833	3.38%

**None of these claims are in the time period Oct 1, 2018 - Sep 30, 2019

Gabapentin – FFS 2016-2019																			
AGENT	**PRODUCT**	**CLAIMS**	**PATIENTS**	**DX A**		**DX N**		**DX R***		**DX B**		**DX C**		**DX D**		**DX E**		**DX G**	
Gabapentin	GABAPENTIN CAP 100MG	**6,617**	**2,123**	249	11.73%	4	0.19%	84	3.96%	264	12.44%	423	19.92%	339	15.97%	109	5.13%	82	3.86%
Gabapentin	GABAPENTIN CAP 300MG	**30,131**	**7,218**	755	10.46%	9	0.12%	299	4.14%	1,085	15.03%	2,020	27.99%	1,605	22.24%	369	5.11%	331	4.59%
Gabapentin	GABAPENTIN CAP 400MG	**5,386**	**1,307**	211	16.14%	5	0.38%	67	5.13%	268	20.51%	537	41.09%	446	34.12%	127	9.72%	104	7.96%
Gabapentin	GABAPENTIN SOL 250/5ML	**1,645**	**209**	101	48.33%	.	.	5	2.39%	13	6.22%	17	8.13%	10	4.78%	5	2.39%	7	3.35%
Gabapentin	GABAPENTIN TAB 600MG	**20,690**	**3,804**	475	12.49%	10	0.26%	168	4.42%	638	16.77%	1,462	38.43%	1,134	29.81%	270	7.10%	237	6.23%
Gabapentin	GABAPENTIN TAB 800MG	**14,565**	**2,470**	345	13.97%	6	0.24%	126	5.10%	429	17.37%	1,194	48.34%	987	39.96%	243	9.84%	210	8.50%
Gabapentin	NEURONTIN CAP 300MG	**2**	**1**	1	100%	.	.	.	.	.	.	.	.	.	.	1	100%	.	.
Gabapentin (Bulk)	GABAPENTIN POW	**1**	**1**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Gabapentin (Once-Daily)	GRALISE TAB 600MG	**1**	**1**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Gabapentin Enacarbil	HORIZANT TAB 600MG ER	**1**	**1**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	TOTALS	**79,039**	**12,999**	1,421	10.93%	21	0.16%	521	4.01%	1,831	14.09%	3,752	28.86%	2,966	22.82%	734	5.65%	631	4.85%

*None of these claims are in the time period Oct 1, 2018 - Sep 30, 2019

Table 6. Prescribers

Specialty ALL

Specialty	RXs
Family Practice	75324
Internal Medicine	23504
Psychiatry	6996
Pediatrics	6779
Physical Medicine and R	6200
Emergency Medicine	6011
Neurology	5619
Anesthesiology	3768
General Practice	1883
Obstetrics-Gynecology	1751
Pulmonary Diseases	1299
Child Psychiatry	1257
General Preventive Medi	1071
Orthopedic Surgery	869
Rheumatology	699
Oncology	424
Infectious Diseases	404
Pediatric Neurology	383
General Surgery	355

Specialty FFS

Specialty	RXs
Family Practice	29749
Internal Medicine	8244
Emergency Medicine	2860
Pediatrics	1976
Physical Medicine and R	1734
Psychiatry	1688
Neurology	1014
General Practice	1004
Obstetrics-Gynecology	769
Anesthesiology	549
Pulmonary Diseases	466
General Preventive Medi	324
Orthopedic Surgery	214
Child Psychiatry	122
Pediatric Neurology	106
Infectious Diseases	98
General Surgery	86
Rheumatology	83
Hematology	66

ALL Credentials

Credentials	RXs
Physician	107174
Nurse Practitioner	41574
Osteopath	23496
QMB-Only Prov	7559
Podiatrist	736
Cert Nurse Midwife	677
Registered Nurse	528
Physical Therapist	170
Cert Social Worker	147
Psychologist	54
Group Practice	43
Physician Assistant	38
Dentist	25
Nurse Anesthetist	11
Oral Surgeons	9
LPN	5
Optometrist	4
Unknown	53536

FFS Credentials

Credentials	RXs
Physician	36476
Nurse Practitioner	14480
Osteopath	9423
QMB-Only Prov	1587
Cert Nurse Midwife	285
Registered Nurse	254
Podiatrist	162
Physical Therapist	100
Cert Social Worker	30
Nurse Anesthetist	11
Physician Assistant	5
Oral Surgeons	4
Dentist	3
LPN	1
Psychologist	1
Unknown	17628

Specialty ALL

Hematology	343
Gastroenterology	151
Cardiology	148
Nephrology	147
Neurological Surgery	140
Endocrinology	106
Geriatrics	103
Gynecology	93
Otorhinolaryngology	92
Dermatology	87
Radiology	82
Plastic Surgery	75
Urology	72
Pathology	67
Ophthalmology	62
Cardiovascular Diseases	59
Neonatology	50
Diagnostic Radiology	49
Radiation Oncology	46
Neuropathology	30
Neuroradiology	27
Cardiovascular Surgery	24
Hand Surgery	18
Thoracic Surgery	18
Diabetes	13
Oncology Surgery	11
Pediatric Surgery	8
Aerospace Medicine	7
Allergy	5
Colon and Rectal Surger	5
Pediatric Cardiology	4
Occupational Medicine	3
Clinical Pathology	1
Unknown	103798

Specialty FFS

Oncology	56
Cardiology	42
Nephrology	40
Gastroenterology	38
Ophthalmology	30
Geriatrics	28
Plastic Surgery	23
Dermatology	22
Otorhinolaryngology	22
Radiology	20
Neurological Surgery	19
Urology	15
Cardiovascular Diseases	12
Gynecology	10
Pathology	9
Radiation Oncology	9
Neonatology	6
Diagnostic Radiology	5
Cardiovascular Surgery	4
Hand Surgery	3
Pediatric Cardiology	3
Thoracic Surgery	3
Colon and Rectal Surger	2
Endocrinology	2
Diabetes	1
Oncology Surgery	1
Unknown	34608

ALL Credentials

FFS Credentials

Appendix 6 – Exploring potential problematic use

Table 1. Number of patients (ALL) by number of prescriptions (in last year) with select diagnoses

	Gabapentin fills (ALL) from Oct 1, 2018 - Sep 30, 2019								
		A	N		B	C	D	E	G
Number of Rxs	**Patients**	**EPILEPSY**	**POSTHERPETIC NEURALGIA**	**RESTLESS LEG SYNDROME**	**ALCOHOL MISUSE**	**DRUG DEPENDENCE**	**DRUG ABUSE**	**POISONING (any substance)**	**ACCIDENTAL POISONING (subset of poisoning)**
1	3134	157	4	49	298	529	416	81	61
2	1773	90	1	47	186	429	306	54	42
3	1294	92	1	24	147	343	246	37	29
4	1007	82	2	23	131	271	195	38	28
5	867	62	1	26	108	260	186	31	16
6	789	61	1	20	76	208	137	31	22
7	731	53	.	13	61	210	140	25	26
8	603	40	4	21	54	142	93	24	15
9	527	48	.	10	44	124	72	16	10
10	539	43	.	16	41	122	69	18	12
11	563	47	1	15	31	95	52	8	7
12	698	73	.	18	40	130	54	16	14
13	433	41	3	7	22	100	49	10	4
14	194	20	.	6	18	47	19	5	6
15	81	5	.	1	7	21	16	4	4
16	42	3	.	.	6	13	5	1	2
17	24	3	.	1	2	8	2	.	1
18	29	5	.	1	4	9	8	3	2
19	25	4	.	2	2	11	7	1	1
20	17	1	.	1	.	6	4	1	.
21	12	1	.	.	3	1	3	1	1
22	14	1	.	.	2	5	1	.	.
23	9	.	.	.	2	3	2	2	.
24	15	2	.	.	.	1	.	.	.
25	5	3	.	.	.	1	.	1	.
26	11	3	.	.	1	4	1	1	1
27	4	1	.	.	.	.	.	.	.
28	2	.	.	.	.	.	.	.	.
29	2	2	.	1	.	1	.	1	.
30	1	.	.	.	.	.	.	.	.
31	1	.	.	.	.	.	.	.	.
32	1	.	.	.	1	1	1	.	.
33	2	1	.	.	.	.	.	.	.
35	1	.	.	.	.	.	.	.	.
36	1	.	.	.	.	.	.	.	.
38	2	.	.	.	.	.	.	.	.
42	1	.	.	.	.	1	.	.	.
47	2	.	.	.	.	.	1	.	.
51	1	.	.	.	.	.	.	.	.
52	1	.	.	.	.	.	.	.	.
78	1	.	.	.	.	.	.	.	.
104	1	1	.	.	.	.	.	.	.
Total	13460								

Table 2. Number of patients (ALL) by number of prescriptions (in last year) that fulfil select criteria

Gabapentin fills (ALL) from Oct 1, 2018 - Sep 30, 2019														
Number of Rxs	Patients	>1 Gabapentin (within 30 days)	>1 Pharmacy (within 30 days)	>1 Prescriber (GABA/Opioid) within 30 days	>3600mg/day*	Patients with >3600mg/day (excluding solutions)◊	>400 days' supply (year)♦	Concurrent pregabalin (within 30 days)* >once	Concurrent opioid (within 30 days)	Concurrent benzodiazepine (within 30 days)	Concurrent opioid and benzo (within 30 days)	Concurrent "muscle relaxant" (within 30 days)	Concurrent hypnotic (within 30 days)	Concurrent opioid+benzo+muscle relaxant+hypnotic (within 30 days)
1	3134	.	.	462	6	6	.	87	779	487	187	474	101	7
2	1773	720	192	321	6	6	.	57	495	310	111	354	94	9
3	1294	784	300	306	4	4	.	45	420	269	106	273	79	5
4	1007	758	388	262	4	4	.	31	362	257	104	263	73	10
5	867	715	394	256	7	6	.	57	353	239	116	228	61	7
6	789	686	436	284	4	4	.	25	359	253	126	233	71	7
7	731	657	570	267	6	6	.	30	342	217	103	240	81	5
8	603	559	390	230	5	5	.	28	287	195	100	229	60	8
9	527	513	486	238	8	8	.	21	295	191	108	205	59	14
10	539	532	464	256	8	8	.	32	315	203	126	215	63	5
11	563	561	536	247	11	10	.	22	313	231	131	216	64	10
12	698	698	756	321	10	10	.	25	407	269	178	276	86	22
13	433	433	578	188	8	8	1	15	247	203	123	192	65	17
14	194	194	478	89	8	8	132	4	106	73	41	85	28	3
15	81	81	238	45	2	2	65	3	50	30	23	43	9	1
16	42	42	164	23	.	.	31	2	25	21	15	22	7	3
17	24	24	108	15	3	3	16	1	16	12	7	10	2	1
18	29	29	220	11	2	2	20	3	12	10	6	10	1	.
19	25	25	186	9	.	.	19	1	11	14	7	11	7	1
20	17	17	126	8	.	.	12	1	9	2	2	8	1	.
21	12	12	114	4	2	2	11	1	4	5	2	4	3	.
22	14	14	108	8	.	.	12	1	8	4	2	2	1	.
23	9	9	82	3	.	.	8	.	4	7	3	3	3	1
24	15	15	96	4	.	.	13	.	6	9	3	8	2	1
25	5	5	58	1	.	.	3	.	2	2	.	1	.	.
26	11	11	136	7	.	.	9	.	8	6	5	5	2	2
27	4	4	8	3	.	.	3	.	4	3	3	3	1	.
28	2	2	2	1	.	.	1	1	2	1	1	.	.	.
29	2	2	.	2	.	.	2	.	2	2	2	1	.	.
30	1	1	.	1	.	.	1	.	1	.	.	.	.	.
31	1	1	32	.	1	1	.	.	.	.	.	1	.	.
32	1	1	48	1	.	.	1	.	1	.	.	1	.	.
33	2	2	106	1	.	.	2	.	1	.	.	1	.	.
35	1	1	2	1	.	.	.	.	1	1	1	.	.	.
36	1	1	.	.	.	.	.	.	.	.	.	.	1	.
38	2	2	12	2	.	.	.	.	2	2	1	1	1	1
42	1	1	28	.	.	.	.	.	.	1	.	.	.	.
47	2	2	14	1	.	.	.	1	1	1	.	1	.	.
51	1	1	.	.	.	.	.	.	1	.	.	.	.	.

Gabapentin fills (ALL) from Oct 1, 2018 - Sep 30, 2019														
Number of Rxs	**Patients**	**>1 Gabapentin (within 30 days)**	**>1 Pharmacy (within 30 days)**	**>1 Prescriber (GABA/Opioid) within 30 days**	**>3600mg/day***	**Patients with >3600mg/day (excluding solutions)◊**	**>400 days' supply (year)♦**	**Concurrent pregabalin (within 30 days)* >once**	**Concurrent opioid (within 30 days)**	**Concurrent benzodiazepine (within 30 days)**	**Concurrent opioid and benzo (within 30 days)**	**Concurrent "muscle relaxant" (within 30 days)**	**Concurrent hypnotic (within 30 days)**	**Concurrent opioid+benzo+muscle relaxant+hypnotic (within 30 days)**
52	1	1	.	1	.	.	1	.	1	1	1	1	.	.
78	1	1	.	1	.	.	1	.	1	.	.	.	.	.
104	1	1	.	.	.	.	1	.	.	1	.	.	1	.
Total	13460													

*Used single prescription to calculate this: (Quantity/day supply) x strength of formulation; this does not capture dosing of patients that received multiple prescriptions overlapping/different strength formulations on separate prescription (underestimate).

◊ It was unclear whether the quantity in the claims data is the actual mL amount.

♦This would be an overestimate if patients received multiple prescriptions overlapping/different strength formulations on separate prescriptions because total days' supply would be counted for each.

***Definition for opioid**

Codeine
Hydrocodone
Hydromorphone
Levorphanol
Meperidine
Morphine
Oxycodone
Oxymorphone
Tapentadol
Tramadol
Fentanyl transdermal patches
Hydrocodone ER
Hydromorphone ER
Methadone
Morphine Sulfate ER
Oxycodone ER
Oxymorphone ER
Tapentadol ER
Tramadol ER

***Definition for benzodiazepine**

Alprazolam
Chlordiazepoxide
Clobazam
Clonazepam
Clorazepate
Diazepam
Estazolam
Flurazepam
Lorazepam
Midazolam
Oxazepam
Quazepam
Temazepam
Triazolam

***Definition for muscle relaxant**

tizanidine
baclofen
carisoprodol
cyclobenzaprine
orphenadrine
methocarbamol
chlorzoxazone
metaxalone

***Definition for Hypnotics (Non-Benzodiazepines, Non-Barbiturates)**

Doxepin
Eszopiclone
Ramelteon
Suvorexant
Tasimelteon
Zaleplon
Zolpidem

Table 3. Number of patients (FFS) by number of prescriptions (in last year) with select diagnoses

	Gabapentin fills (FFS) from Oct 1, 2018 - Sep 30, 2019								
		A	N		B	C	D	E	G
Number of Rxs	Patients	EPILEPSY	POSTHERPETIC NEURALGIA	RESTLESS LEG SYNDROME	ALCOHOL MISUSE	DRUG DEPENDENCE	DRUG ABUSE	POISONING (any substance)	ACCIDENTAL POISONING (subset of poisoning)
1	2104	145	2	47	281	496	404	70	57
2	1144	79	1	41	166	391	300	47	39
3	796	62	1	19	128	297	218	32	30
4	603	52	2	20	108	219	165	28	25
5	508	44	1	22	92	208	156	24	13
6	387	44	1	19	58	147	112	19	19
7	345	45	.	16	42	149	106	17	17
8	270	31	2	12	39	105	80	13	13
9	210	25	1	9	32	78	54	7	6
10	189	25	.	12	29	80	50	7	9
11	181	28	.	13	19	54	44	2	4
12	213	39	.	12	30	77	35	11	10
13	115	26	3	6	12	47	31	3	3
14	64	13	.	4	10	23	13	2	3
15	24	3	.	1	5	9	8	2	2
16	12	2	.	.	4	5	4	.	1
17	8	1	.	.	2	3	.	.	.
18	6	3	.	.	2	6	5	2	1
19	10	2	.	1	1	4	5	.	.
20	7	1	.	1	.	5	4	1	.
21	3	1	.	.	2	.	3	.	.
22	3	1	.	.	1	1	.	.	.
23	2	1	.	.	.	.	.	.	.
24	6	3	.	.	.	2	.	1	.
25	2	1	.	.	.	.	.	.	.
26	2	1	.	.	.	1	.	.	1
27	3	1	.	.	.	.	.	.	.
29	3	2	.	1	.	1	.	1	.
33	1	1	.	.	.	.	.	.	.
36	1	.	.	.	.	.	.	.	.
47	1	.	.	.	.	.	.	.	.
51	1	.	.	.	.	.	.	.	.
52	1	.	.	.	.	.	.	.	.
78	1	.	.	.	.	.	.	.	.
104	1	1	.	.	.	.	.	.	.
Total	7227								

Table 4. Number of patients (FFS) by number of prescriptions (in last year) that fulfil select criteria

Gabapentin fills (FFS) from Oct 1, 2018 - Sep 30, 2019													
Number of Rxs	Patients	>1 Gabapentin (within 30 days)	>1 Pharmacy (within 30 days)	>1 Prescriber (GABA/Opioid) within 30 days	>3600mg/ day*	>400 days' supply (year)	Concurrent pregabalin (within 30 days)* on >one occasion	Concurrent opioid (within 30 days)*	Concurrent benzodiazepine (within 30 days)*	Concurrent opioid and benzo (within 30 days)	Concurrent "muscle relaxant" (within 30 days)*	Concurrent hypnotic within 30 days)*	Concurrent opioid+benzo +muscle relaxant+hypnotic (within 30 days)
1	2104	.	.	240	6	.	48	404	315	92	308	56	3
2	1144	534	170	151	5	.	33	248	200	58	217	55	4
3	796	534	212	139	2	.	22	209	144	48	153	39	.
4	603	482	266	129	3	.	22	190	147	48	157	41	4
5	508	456	272	119	5	.	32	165	113	44	124	28	4
6	387	347	270	120	1	.	14	154	115	51	103	25	.
7	345	317	336	110	3	.	15	143	100	49	107	29	2
8	270	253	190	84	3	.	18	108	89	41	93	26	.
9	210	205	268	76	5	.	9	97	66	30	75	12	2
10	189	187	260	78	1	.	11	95	65	36	66	19	2
11	181	180	278	76	2	.	5	97	68	39	64	17	4
12	213	213	306	82	1	.	7	106	63	35	78	16	3
13	115	115	180	37	3	.	3	54	49	25	49	13	4
14	64	64	156	26	2	45	2	34	27	17	27	8	.
15	24	24	92	9	.	15	1	12	7	4	13	1	.
16	12	12	50	7	.	8	.	9	5	5	6	.	.
17	8	8	28	6	2	2	.	6	4	1	3	.	.
18	6	6	54	1	.	3	2	1	1	1	2	.	.
19	10	10	118	3	.	6	1	5	4	2	4	3	.
20	7	7	70	5	.	4	.	5	1	1	4	.	.
21	3	3	40	1	.	3	.	1	.	.	.	1	.
22	3	3	20	1	.	2	.	1	.	.	.	.	.
23	2	2	.	.	.	1	.	.	1	.	.	.	.
24	6	6	82	4	.	5	.	5	3	3	4	1	.
25	2	2	.	.	.	1	.	1	1	.	1	.	.
26	2	2	.	2	.	.	.	2	1	1	2	.	.
27	3	3	8	3	.	2	.	3	2	2	3	.	.
29	3	3	.	3	.	3	.	3	2	2	1	.	.
33	1	1	.	1	.	1	.	1	.	.	1	.	.
36	1	1	.	.	.	.	.	.	.	.	.	1	.
47	1	1	.	.	.	.	.	.	1	.	.	.	.
51	1	1	.	.	.	.	.	1	.	.	.	.	.
52	1	1	.	1	.	1	.	1	1	1	1	.	.
78	1	1	.	1	.	1	.	1	.	.	.	.	.
104	1	1	.	.	.	1	.	.	1	.	.	1	.
Total	7227												

*Used single prescription to calculate this: (Quantity/day supply) x strength of formulation; this would not capture dosing of patients that received multiple prescriptions overlapping/different strength formulations on separate prescription (underestimate). ◊It was unclear whether the quantity in the claims data is the actual mL amount etc. ♦This would be an overestimate if patients received multiple prescriptions overlapping/different strength formulations on separate prescriptions.

Table 5. Prescribers of patients with >400 days' supplied♦ from Oct 1, 2018 - Sep 30, 2019

Specialty ALL

Specialty	RXs
Family Practice	5132
Internal Medicine	1400
Psychiatry	597
Physical Medicine and R	562
Neurology	447
Pediatrics	443
Anesthesiology	222
Emergency Medicine	196
Pulmonary Diseases	172
Child Psychiatry	125
Rheumatology	115
Obstetrics-Gynecology	73
General Preventive Medi	72
General Practice	54
Neonatology	39
Orthopedic Surgery	23
Pediatric Neurology	18
Oncology	14
General Surgery	9
Ophthalmology	5
Gastroenterology	3
Geriatrics	2
Gynecology	2
Otorhinolaryngology	2
Cardiology	1
Neurological Surgery	1
Unknown	6510

Specialty FFS

Specialty	RXs
Family Practice	1688
Internal Medicine	570
Physical Medicine and R	144
Pediatrics	140
Emergency Medicine	89
Psychiatry	59
Pulmonary Diseases	53
Child Psychiatry	32
Neurology	27
Anesthesiology	25
General Practice	21
Obstetrics-Gynecology	10
Orthopedic Surgery	7
Rheumatology	6
Ophthalmology	5
General Preventive Medi	4
Gastroenterology	3
Geriatrics	2
Pediatric Neurology	2
Neurological Surgery	1
Unknown	1309

ALL Credentials

Credentials	RXs
Physician	7235
Nurse Practitioner	2996
Osteopath	1596
QMB-Only Prov	717
Cert Nurse Midwife	39
Registered Nurse	11
Physical Therapist	5
Podiatrist	3
Cert Social Worker	1
Unknown	2799

FFS Credentials

Credentials	RXs
Physician	1965
Nurse Practitioner	695
Osteopath	641
QMB-Only Prov	70
Cert Nurse Midwife	31
Unknown	504

♦This would be an overestimate if patients received multiple prescriptions overlapping/different strength formulations on separate prescriptions.

Table 6. Diagnosis codes submitted for potential inappropriate gabapentin use/prescribing/patients at increased risk for adverse outcomes

Gabapentin fills (ALL) from Oct 1, 2018 - Sep 30, 2019	NUMBER OF PATIENTS WITH THESE DX								
		A		N	B	C	D	E	G
	Any dx	**EPILEPSY**	**RESTLESS LEG SYNDROME**	**POSTHERPETIC NEURALGIA**	**ALCOHOL MISUSE**	**DRUG DEPENDENCE**	**DRUG ABUSE**	**POISONING (any substance)**	**ACCIDENTAL POISONING (subset of poisoning)**
>1 Prescriber (GABA/Opioid) within 30 days	1622	463	158	9	420	998	609	205	151
>1 Pharmacy (within 30 days	1140	272	86	3	350	830	627	171	137
Patients with >3600mg/day*	55	21	3	1	7	42	26	9	9
Patients with >400 days' supply (year)♦	184	49	14	0	39	127	75	31	19
PATIENTS WITH Concurrent opioid (within 30 days)*	2065	562	204	11	520	1259	753	247	192
PATIENTS WITH Concurrent PREGABALIN(within 30 days)*	258	70	23	1	63	181	119	32	29
PATIENTS WITH Concurrent benzodiazepine (within 30 days	1724	571	117	4	472	1062	690	259	202
Patient with concurrent opioid and benzo (within 30 days)	777	281	61	2	163	483	260	108	87
Patient with concurrent muscle relaxant (within 30 days)	1544	428	148	12	387	940	582	189	145
Patient with concurrent hypnotic within 30 days)*	439	114	41	2	96	285	161	80	59
Patient with concurrent opioid+benzo+muscle relaxant+hypnotic	63	25	7	0	9	38	17	10	6

*Used single prescription to calculate this: (Quantity/day supply) x strength of formulation; this would not capture dosing of patients that received multiple prescriptions overlapping/different strength formulations on separate prescription (underestimate).

♦This would be an overestimate if patients received multiple prescriptions overlapping/different strength formulations on separate prescriptions.

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